Cochrane Library

Cochrane Database of Systematic Reviews

Progestagens and anti-progestagens for pain associated with endometriosis (Review)

Brown J, Kives S, Akhtar M

Brown J, Kives S, Akhtar M.
Progestagens and anti-progestagens for pain associated with endometriosis.
Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD002122.
DOI: 10.1002/14651858.CD002122.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Progestagens and anti-progestagens for pain associated with endometriosis

Julie Brown[1], Sari Kives[2], Muhammad Akhtar[3]

[1]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [2]Obstetrics & Gynecology, St Michaels Hospital, Toronto, Canada. [3]Clinical Reproductive Medicine Unit, University Hospitals, Coventry & Warwickshire NHS Trust, Coventry, UK

Contact address: Julie Brown, Obstetrics and Gynaecology, University of Auckland, FMHS, Auckland, New Zealand. j.brown@auckland.ac.nz.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2012.

Citation: Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD002122. DOI: 10.1002/14651858.CD002122.pub2.

ABSTRACT

Background

Endometriosis is a chronic inflammatory condition defined by the presence of glands and stroma outside the uterine cavity. It occurs in 7% to 10% of all women of reproductive age and may present as pain or infertility. The pelvic pain may be in the form of dysmenorrhoea, dyspareunia or pelvic pain. Initially a combination of estrogens and progestagens was used to create a pseudopregnancy and alleviate the symptoms associated with endometriosis. Progestagens alone or anti-progestagens have been considered as alternatives because they are inexpensive and may have a better side effect profile than other choices.

Objectives

To determine the effectiveness of both the progestagens and anti-progestagens in the treatment of painful symptoms ascribed to the diagnosis of endometriosis.

Search methods

We used the search strategy of the Menstrual Disorders and Subfertility Group to identify all publications which described or might have described randomised controlled trials (RCTs) of any progestagen or any anti-progestagen in the treatment of symptomatic endometriosis. We updated the review in 2011.

Selection criteria

We considered only RCTs which compared the use of progestagens and anti-progestagens with other interventions, placebo or no treatment for the alleviation of symptomatic endometriosis.

Data collection and analysis

We have added six new studies, bringing the total of included studies to 13 in the update of this review. The six newly included studies evaluated progestagens (comparisons with placebo, danazol, oral or subdermal contraceptive, oral contraceptive pill and danazol, gonadotrophin-releasing hormone (GnRH) analogue and other drugs). The remaining studies compared the anti-progestagen gestrinone with danazol, GnRH analogues or itself.

Main results

The progestagen medroxyprogesterone acetate (100 mg daily) appeared to be more effective at reducing all symptoms up to 12 months of follow-up (MD -0.70, 95% CI -8.61 to -5.39; P < 0.00001) compared with placebo. There was evidence of significantly more cases of acne

(six versus one) and oedema (11 versus one) in the medroxyprogesterone acetate group compared with placebo. There was no evidence of a difference in objective efficacy between dydrogesterone and placebo.

There was no evidence of a benefit with depot administration of progestagens versus other treatments (low dose oral contraceptive or leuprolide acetate) for reduced symptoms. The depot progestagen group experienced significantly more adverse effects.

There was no overall evidence of a benefit of oral progestagens over other medical treatment at six months of follow-up for self-reported efficacy. Amenorrhoea and bleeding were more frequently reported in the progestagen group compared with other treatment groups.

There was no evidence of a benefit of anti-progestagens (gestrinone) compared with danazol. GnRH analogue (leuprorelin) was found to significantly improve dysmenorrhoea compared with gestrinone (MD 0.82, 95% CI 0.15 to 1.49; P = 0.02) although it was also associated with increased hot flushes (OR 0.20, 95% CI 0.06 to -0.63; P = 0.006).

Authors' conclusions

There is only limited evidence to support the use of progestagens and anti-progestagens for pain associated with endometriosis.

PLAIN LANGUAGE SUMMARY

Progestagens and anti-progestagens for pain associated with endometriosis

Endometriosis is a painful condition where tissue from the lining of the womb (uterus) is found outside the uterus as well. It can cause pain in the abdomen, generally and during periods (menstruation) or sex. Endometriosis can also lead to infertility. Treatments include surgery or drugs to try and shrink the tissue. Progestagens and anti-progestagens are some of the hormonal drugs used for treatment. This systematic review of trials found limited evidence for the effectiveness of these drugs in the reduction of pain from endometriosis. This was due to the limited number of randomised controlled trials comparing each drug.

Summary of findings for the main comparison. Progestagen compared to placebo for pain associated with endometriosis

Progestagen compared to placebo for pain associated with endometriosis

Patient or population: patients with pain associated with endometriosis
Settings: gynaecology clinics
Intervention: progestagen
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Progestagen				
AFS score	The mean AFS score in the control groups was **1.76**	The mean AFS score in the intervention groups was **0.58 lower** (1.41 lower to 0.25 higher)		33 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Patient assessed efficacy, sum of all symptoms Follow-up: mean 6 months	The mean patient assessed efficacy, sum of all symptoms in the control groups was **-5.20**	The mean patient assessed efficacy, sum of all symptoms in the intervention groups was **5.2 lower** (6.8 to 3.6 lower)		33 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Patient assessed efficacy, sum of all symptoms Follow-up: mean 12 months	The mean patient assessed efficacy, sum of all symptoms in the control groups was **-7.0**	The mean patient assessed efficacy, sum of all symptoms in the intervention groups was **7 lower** (8.61 to 5.39 lower)		29 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Side effects - acne	**59 per 1000**	**375 per 1000** (59 to 852)	**OR 9.6** (1 to 91.96)	33 (1 study)	⊕⊝⊝⊝ **very low** [1,2,3]	
Side effects - oedema	**59 per 1000**	**688 per 1000** (184 to 956)	**OR 35.2** (3.6 to 344.19)	33 (1 study)	⊕⊝⊝⊝ **very low** [1,2,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] There was an unclear explanation for randomisation, allocation concealment and blinding
[2] Evidence based on a single trial
[3] Summary effect crosses line of no effect and substantive harm or benefit
[4] Wide confidence intervals indicative of imprecision

Summary of findings 2. Depot progestagen compared to other treatment for pain associated with endometriosis

Depot progestagen compared to other treatment for pain associated with endometriosis

Patient or population: patients with pain associated with endometriosis
Settings: gynaecology clinics
Intervention: depot progestagen
Comparison: other treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other treatment	Depot progestagen				
Improvement in dysmenorrhoea Follow-up: mean 6 months	**978 per 1000**	**895 per 1000** (692 to 969)	**OR 0.19** (0.05 to 0.69)	274 (1 study)	⊕⊕⊝⊝ **low** [1,2]	
Improvement in dysmenorrhoea Follow-up: mean 12 months	**768 per 1000**	**676 per 1000** (551 to 782)	**OR 0.63** (0.37 to 1.08)	274 (1 study)	⊕⊕⊝⊝ **low** [2,3]	
Side effects - hot flushes	**90 per 1000**	**29 per 1000** (11 to 76)	**OR 0.3** (0.11 to 0.83)	354 (2 studies)	⊕⊕⊝⊝	

					low [4,5]
Side effects - amenorrhoea	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 21.18** (1.18 to 380.9)	80 (1 study)	⊕⊝⊝⊝ **very low** [1,2,6]
Side effects - breakthrough bleeding/spotting	**28 per 1000**	**373 per 1000** (157 to 655)	**OR 20.56** (6.44 to 65.56)	354 (2 studies)	⊕⊕⊝⊝ **low** [1,4]
Side effects - bloating	**275 per 1000**	**625 per 1000** (393 to 811)	**OR 4.39** (1.71 to 11.3)	80 (1 study)	⊕⊝⊝⊝ **very low** [1,2,6]
Side effects - injection site reaction	**0 per 1000**	**0 per 1000** (0 to 0)	**OR 20.64** (1.19 to 358.23)	274 (1 study)	⊕⊕⊝⊝ **low** [1,2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Wide confidence intervals indicate some imprecision
[2] Evidence based on a single trial
[3] Summary effect crosses line of no effect and substantive benefit or harm
[4] One of the trials was open label and attrition was not adequately explained
[5] I square statistic was 66%
[6] Trial was open label and inadequately explained attrition

Summary of findings 3. Oral progestagens versus other treatment for pain associated with endometriosis

Oral progestagens versus other treatment for pain associated with endometriosis

Patient or population: patients with pain associated with endometriosis
Settings:
Intervention: oral progestagens versus other treatment

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk			
	Control	**Oral progestagens versus other treatment**			
Patient assessed efficacy - pain Follow-up: mean 6 months	The mean patient assessed efficacy - pain in the control groups was **21.1**	The mean patient assessed efficacy - pain in the intervention groups was **0.1 higher** (0.26 lower to 0.46 higher)		286 (2 studies)	⊕⊕⊕⊖ **moderate** [1]
Objective efficacy at end of follow up (12 months) - AFS score	The mean objective efficacy at end of follow up (12 months) - AFS score in the control groups was **1.31**	The mean objective efficacy at end of follow up (12 months) - AFS score in the intervention groups was **0.34 higher** (0.01 lower to 0.7 higher)		302 (2 studies)	⊕⊕⊕⊖ **moderate** [2]
Side effects - headache	**244 per 1000**	**158 per 1000** (109 to 220)	**OR 0.58** (0.38 to 0.87)	613 (3 studies)	⊕⊕⊕⊖ **moderate** [1]
Side effects - hot flushes	**306 per 1000**	**178 per 1000** (120 to 251)	**OR 0.49** (0.31 to 0.76)	613 (3 studies)	⊕⊕⊖⊖ **low** [1,3]
Side effects - genital bleeding	**634 per 1000**	**891 per 1000** (811 to 939)	**OR 4.69** (2.47 to 8.9)	271 (1 study)	⊕⊕⊖⊖ **low** [4,5]
Side effects - amenorrhoea	**387 per 1000**	**758 per 1000** (645 to 843)	**OR 4.95** (2.88 to 8.52)	252 (1 study)	⊕⊖⊖⊖ **very low** [4,5,6]
Sleep disorder	**78 per 1000**	**16 per 1000** (3 to 71)	**OR 0.19** (0.04 to 0.90)	252 (1 study)	⊕⊖⊖⊖ **very low** [4,5,6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] One trial did not provide adequate explanation for randomisation, allocation concealment or blinding and the other trial was open label
[2] One trial did not explain adequately details for allocation concealment, randomisation and blinding

[3] I^2 statistic was 65%
[4] Wide confidence intervals, indicative of imprecision
[5] Evidence based on a single
[6] Open label trial

Summary of findings 4. Anti-progestagen compared to other treatment for pain associated with endometriosis

Anti-progestagen compared to other treatment for pain associated with endometriosis

Patient or population: patients with pain associated with endometriosis
Settings: gynaecology clinics
Intervention: anti-progestagen
Comparison: other treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	other treatment	Anti-progestagen				
Patient assessed efficacy none or mild painful periods (dysmenorrhoea) Follow-up: mean 6 months	**667 per 1000**	**673 per 1000** (524 to 794)	**OR 1.03** (0.55 to 1.93)	176 (2 studies)	⊕⊕⊝⊝ **low** [1]	
Objective assessment of efficacy at end of treatment (6 months) - rAFS scores	The mean objective assessment of efficacy at end of treatment (6 months) - rAFS scores in the control groups was **11.8**	The mean objective assessment of efficacy at end of treatment (6 months) - rAFS scores in the intervention groups was **1.4 higher** (6.76 lower to 9.56 higher)		16 (1 study)	⊕⊝⊝⊝ **very low** [2,3,4]	
Patient assessed efficacy painful periods visual analogue scale Follow-up: mean 12 months	The mean patient assessed efficacy painful periods in the control groups was **4.76**	The mean patient assessed efficacy painful periods in the intervention groups was **3 lower** (4.79 to 1.21 lower)		55 (1 study)	⊕⊕⊕⊝ **moderate** [4]	
Side effects - seborrhoea	**204 per 1000**	**413 per 1000** (303 to 534)	**OR 2.74** (1.69 to 4.46)	357 (3 studies)	⊕⊕⊝⊝	

					low [1]
Side effects - hirsutism	**248 per 1000**	**465 per 1000** (346 to 588)	**OR 2.63** (1.6 to 4.32)	302 (2 studies)	⊕⊖⊖⊖ **very low** [1,5]
Side effects - hot flushes	**464 per 1000**	**360 per 1000** (267 to 462)	**OR 0.65** (0.42 to 0.99)	357 (3 studies)	⊕⊖⊖⊖ **very low** [1,6]
Side effects - amenorrhoea	**962 per 1000**	**500 per 1000** (200 to 905)	**OR 0.04** (0.01 to 0.38)	49 (1 study)	⊕⊕⊖⊖ **low** [3,4]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Inadequate explanation of randomisation and allocation concealment, one of the trials was open label
[2] Open label trial with inadequate allocation concealment
[3] Wide confidence intervals indicative of imprecision
[4] Evidence based on a single trial
[5] I^2 statistic was 68%
[6] I^2 statistic was 78%

BACKGROUND

Description of the condition

Endometriosis is a chronic inflammatory condition defined by the presence of glands and stroma outside the uterine cavity. It occurs in 7% to 10% of all women of reproductive age and may present as pain or infertility (Wheeler 1989).

Endometriosis presents either with the problem of infertility (Haney 1993; Prentice 1996) or with painful symptoms (Barlow 1993). The painful symptoms may take the form of dysmenorrhoea (painful periods), dyspareunia (pain during or after sexual intercourse) or pelvic or lower abdominal pain. Typically the pain precedes the onset of menses and lasts for the duration of the cycle. Less commonly patients also present with cyclical pain at other sites, relating to endometriosis at extra-pelvic sites (Augoulea 2008; Lancaster 1995). Although the exact incidence of endometriosis is unknown, endometriosis is a significant problem for the affected individual and the cost of the disease is high both in human and economic terms (Mathias 1996).

Description of the intervention

The clinical observation of an apparent resolution of symptoms during pregnancy gave rise to the concept of treating patients with a pseudopregnancy regime (Kistner 1959). Initially combinations of high dose estrogens and progestagens were used, but this was subsequently replaced by progestagens alone (Kistner 1958). More recently anti-progestagens have been developed and they have also been employed in the treatment of endometriosis (Thomas 1987a). The main side effects of progestagens include irregular menstrual cycles or cessation of menstruation, weight gain and breast tenderness. Cytoproterone acetate is associated with liver toxicity. The main side effects associated with anti-progesterones include breakthrough bleeding, acne, fluid retention, weight gain and other androgenic symptoms.

How the intervention might work

The precise pathogenesis (mode of development) of endometriosis remains unclear, but it is evident that endometriosis arises by the dissemination of endometrium to ectopic sites (sites other than its normal location within the uterus) and the subsequent establishment of deposits of ectopic endometrium (Kruitwagen 1993; McLaren 1996). The assumption is made that these deposits of ectopic endometrium are responsible for the symptoms of endometriosis. Conventional treatments, therefore, are directed at the removal of all ectopic tissue. Surgical treatments achieve this by destroying or removing the implant, whilst medical therapies induce atrophy within the hormonally dependent ectopic endometrium so that they shrink in size and number.

Medical treatments theoretically have the ability to treat those implants not visible to the naked eye. Traditionally the oral contraceptive pill has been first line treatment for patients with presumed endometriosis (Davis 2007). Progestagens alone, however, can induce decidualisation (an adaption of the uterus to enable implantation of the embryo), atrophy of implants and resolution of symptoms. The progestagens result in the creation of a pseudopregnancy. The clinical observation of apparent resolution of symptoms of endometriosis during pregnancy gave rise to treatment with a medication containing a progestagen (Moghissi 1990). Gonadotrophin-releasing hormone analogues and danazol are also used for the treatment of endometriosis but have a less favourable profile in terms of safety, tolerability and cost (Rodgers 2008). Anti-progestagens are a substance that prevents cells from making or using progesterone. They may also be beneficial in treating endometriosis as they display anti-proliferative effects in the endometrium but serum estradiol levels remain in the early to mid-follicular phase range. For this reason they avoid the bone loss and hypoestrogenism associated with progestagens alone (Spitz 2003).

Why it is important to do this review

Progestagens are readily available, inexpensive and may have a better side effect profile than other choices (such as danazol), and antiprogestagens may have even fewer side effects. This review evaluates the role of both progestagens and anti-progestagens in the treatment of symptomatic endometriosis.

OBJECTIVES

To determine the effectiveness and adverse effects of both progestagens and anti-progestagens in the treatment of painful symptoms associated with endometriosis.

METHODS

Criteria for considering studies for this review

Types of studies

We have included only randomised controlled trials (RCTs) which compared the use of progestagens and anti-progestagens in the treatment of symptomatic endometriosis. We considered trials with placebo arms, no treatment arms and comparison to other medical therapies or surgical therapies, but have analysed these separately. We have not included quasi-RCTs.

Types of participants

This review considered studies that included women of reproductive years with painful symptoms and a laparoscopic diagnosis of endometriosis.

We considered painful symptoms associated with endometriosis as follows: cyclical pain associated with menstruation (dysmenorrhoea), or not associated with menstruation; deep dyspareunia (pain during or following sexual intercourse); lower abdominal or pelvic pain of a non-cyclical nature; pain on defecation; and any other painful symptom ascribed to endometriosis that was studied in any trial. We included all studies, whether the duration of symptoms was specified (three or six months) or not.

We excluded trials where participants had asymptomatic disease or infertility alone.

Types of interventions

We considered only those treatments where the aim was to achieve symptom control through disease resolution either medically or postoperatively regardless of dose, route of administration or duration of treatment.

Depomedroxyprogesterone acetate, cytoproterone acetate, medroxyprogesterone acetate, gestagen and dienogest were all evaluated in the literature as different progestagens for the

treatment of endometriosis. Gestrinone was the only anti-progestagen identified that has been evaluated for the treatment of endometriosis.

The comparisons considered were head-to-head drug comparisons, conservative surgery, non-steroidal anti-inflammatories, placebo or no treatment, oral contraceptive or danazol or GNRHa.

We did not consider any trial where the symptom relief was not documented, either through an objective or subjective measure, or if the surgical procedure was not conservative. We also excluded alternative or complementary therapies.

We have not included any trial where the progesterone intrauterine system was used as a treatment for endometriosis as a separate Cochrane Review addresses this question. Similarly we have not included any trial where danazol was used as a treatment as a separate Cochane Review addresses this.

Types of outcome measures

Primary outcomes

We considered relief or reduction of symptoms of endometriosis, measured either subjectively or objectively, for each pain symptom when possible. We considered outcomes measures at the end of the treatment and, when possible, at three, six, nine, 12 and 18 months following completion of treatment.

- Subjective outcome: relief of any or all symptoms of endometriosis using quantitative measures such as visual analogue scales or qualitative measures such as cured, better, same, or worse.
- Objective outcome: resolution of endometriotic implants assessed by either the revised American Fertility Society (AFS) score or implant score. Although this is neither a direct or indirect measure of pain, it is an independent assessment of disease resolution.

Secondary outcomes

We considered the occurrence of any adverse effects either during treatment or following treatment.

Search methods for identification of studies

Electronic searches

We utilised the search strategy of the Menstrual Disorders and Subfertility Group to identify all publications which described or might have described RCTs of any progestagen or anti-progestagen in the treatment of symptomatic endometriosis (refer to Appendix 1). For a full outline of the Review Group search strategy see Review Group details.

In addition, we conducted electronic searches in the following electronic databases:

1) CENTRAL (Appendix 2) (to 23 August 2011);

2) MEDLINE (Appendix 3) (1950 to 23 August 2011);

3) EMBASE (Appendix 4) (1980 to 23 August 2011);

4) PsycINFO (Appendix 5) (1806 to 23 August 2011).

CINAHL was not searched in the 2011 update.

Searching other resources

We searched conference proceedings and reference lists of retrieved articles, and also contacted authors for additional information and data.

Data collection and analysis

Selection of studies

Two review authors (SK, JB) independently selected studies. Where uncertainty existed regarding suitability for inclusion, or discrepancy existed between the initial two authors, a third author made a further assessment. If required, we sought additional information from the principal or corresponding investigator of the trial.

Data extraction and management

The same two assessors extracted data; at least one of the assessors was an expert in the content matter. For data extraction, we used forms developed according to Cochrane guidelines. In some papers data were presented in graphical form. Where this was the case, we have approached the authors for clarification and, if necessary, extracted the data from the graphs.

Assessment of risk of bias in included studies

We assessed the quality of trials for inclusion using a standard risk of bias checklist (refer to Figure 1 and Figure 2). We collected the following information: the method of randomisation, allocation concealment, blinding, completeness of data and selective reporting. Both JB and SK extracted this information independently and resolved disagreements through consensus.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

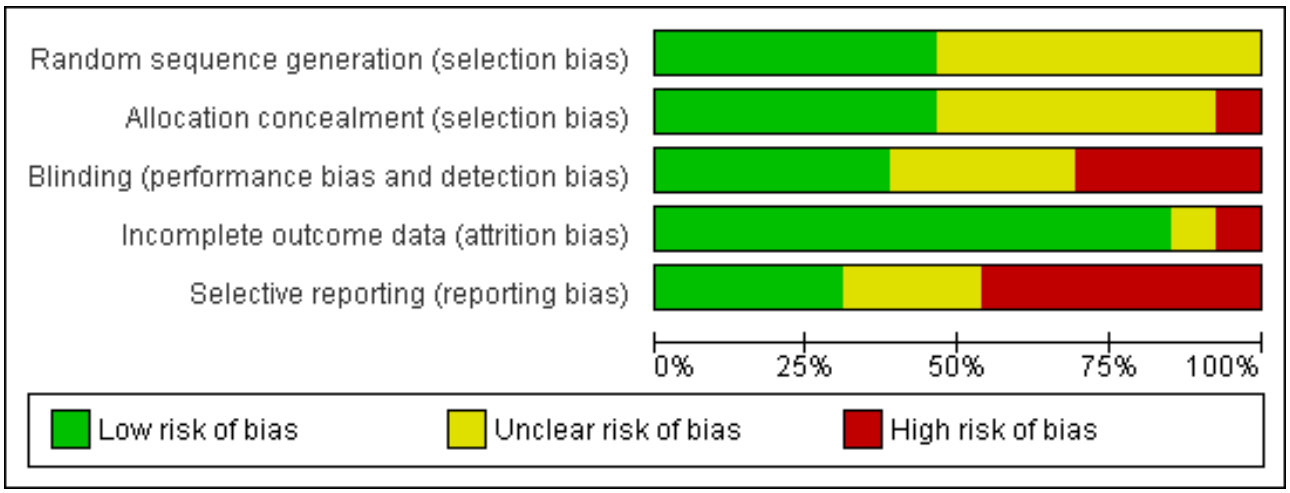
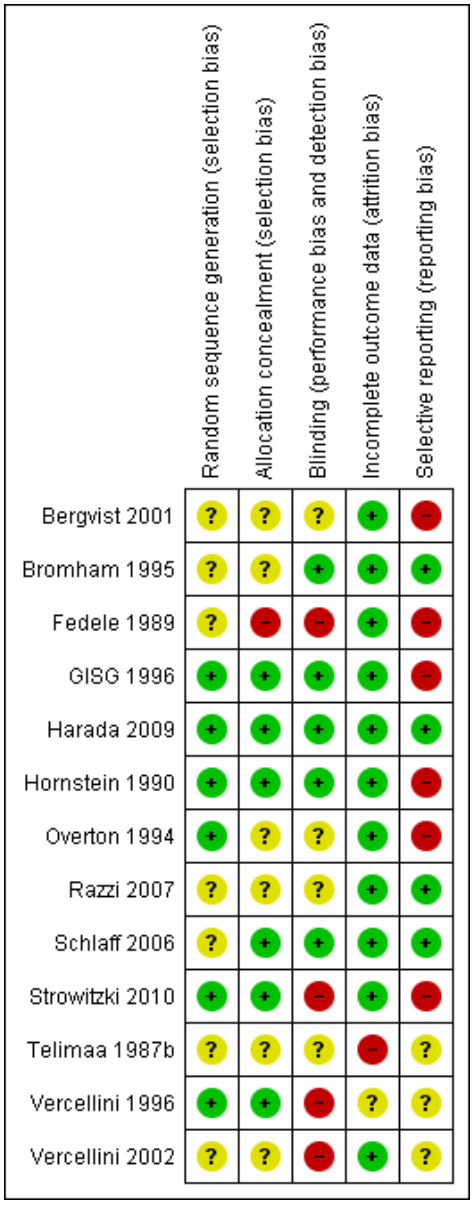


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

We performed statistical analyses according to the statistical guidelines for review authors in the Menstrual Disorders and Subfertility Review Group. We used relative risk as the measure of effect for dichotomous data. For continuous data, we used weighted differences whenever outcomes were measured in a standard way across studies. However, as many different methods exist for assessing pain, we used standardised mean differences when comparing multiple methods. Although different methods give different absolute values, they are conceptually measuring the same parameter. We considered the different methods of measuring pain together, not subjected to separate subgroup analyses. Where there were sufficient data, we calculated a summary statistic for each outcome using a fixed-effect model.

Unit of analysis issues

We presented data as per woman randomised and there were no anticipated concerns over unit of analysis issues between studies.

Dealing with missing data

We requested from the original authors any data that could not be analysed because they were in graph form or were missing. We planned a sensitivity analysis if significant data were missing.

Assessment of heterogeneity

We noted heterogeneity in the data and cautiously explored it using the previously identified characteristics of the studies, particularly assessments of quality. We undertook sensitivity analyses to examine the viability of the results in relation to a number of factors including study quality and the source of the data (published

or unpublished). See the Review Group module details for more information. We determined statistical heterogeneity using the I^2 statistic.

Assessment of reporting biases

There were insufficient studies to determine the existence of publication bias via a funnel plot. However, the review authors have attempted to obtain data from unpublished as well as published sources.

Data synthesis

We carried out meta-analysis using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Data for pain associated with endometriosis are often presented as an overall score and then subgrouped according to pelvic pain, dysmenorrhoea and dyspareunia. Data were also subgrouped according to whether pain was objectively or subjectively determined.

Sensitivity analysis

Where heterogeneity was more than 50%, we considered sensitivity analysis based on the quality of the individual trials to attempt to explain it.

RESULTS

Description of studies

Results of the search

We identified 26 studies as possibilities for inclusion in the systematic review. We identified nine additional studies in this 2011 Cochrane Review update.

Included studies

We have included a total of 13 studies in this 2011 Cochrane Review update (Bergvist 2001; Bromham 1995; Fedele 1989; GISG 1996; Harada 2009; Hornstein 1990; Overton 1994; Razzi 2007; Schlaff 2006; Strowitzki 2010; Telimaa 1987b; Vercellini 1996; Vercellini 2002). There were seven studies in the last published version from 2000.

Progestagens

We identified eight RCTs that considered the role of progestagens alone in the treatment of endometriosis (Bergvist 2001; Harada 2009; Overton 1994; Razzi 2007; Schlaff 2006; Strowitzki 2010; Vercellini 1996; Vercellini 2002). We identified other studies but excluded them because many participants had received operative treatment at the time of study entry, the drug formulation was unknown, or the patients studied were too specific (see Characteristics of excluded studies). We included one study although a small percentage of patients had received operative treatment at the time of diagnostic laparoscopy (Telimaa 1987b).

Overton 1994 considered three groups of women with endometriosis who wished to achieve pregnancy but also complained of pain. Patients were randomised to two doses of dydrogesterone (40 mg or 60 mg) once daily or placebo. The endpoints of this study that were relevant to this review were the reduction in pain scores (derived from diary cards) and the reduction in the AFS score at second look laparoscopy (performed within three months of completing treatment). Only 39 out of 62 women completed the study and underwent a second look laparoscopy.

Vercellini 1996 compared 150 mg of depot medroxyprogesterone every three months with a 20 µg oral contraceptive pill (OCP) with 50 mg danazol. Both the pill and danazol were taken for three weeks out of four. The primary endpoint was the degree of satisfaction at the end of therapy. A change in severity of symptoms was also measured using a 10 cm visual analogue score and a 0 to 3 point verbal rating scale.

Vercellini 2002 similarly compared 12.5 mg cytoproterone acetate once daily versus a continuous monophasic OCP once daily (0.02 µg ethinyl estradiol and 0.15 mg desogestrel). The primary endpoint, as in their previous study, was the degree of satisfaction at the end of therapy. A change in severity of symptoms was also measured by a 100 mm visual analogue score and a 0 to 3 point verbal rating scale.

Bergvist 2001 compared 15 mg medroxyprogesterone twice daily versus 200 µg nafarelin intranasally twice daily. Each group also received a placebo nasal spray or placebo tablets. In this way each group took the same number of tablets daily as the those in the active medroxyprogesterone group and the same number of nasal sprays as those in the active nafarelin group. The endpoint relevant to this review was the endometriosis severity score. Of the 48 who participated only 30 competed the study.

Schlaff 2006 compared 104 mg subcutaneous depot medroxyprogesterone every three months versus 11.25 mg leuprolide intramuscularly (IM) every three months. The primary endpoint was the reduction in five endometriosis symptoms or signs. Of the 274 participants only 190 completed the six months of active treatment.

Razzi 2007 compared desogestrel 75 µg daily with ethinylestridiol plus desogestrel daily for six months in 40 women with Stage I to III endometriosis. The primary endpoint was self-reported pain using a visual analogue scale.

Strowitzki 2010 compared 2 mg of dienogest daily with leuprolide acetate 3.75 mg depot (IM four weekly) for six months in 252 women with Stage I to IV endometriosis. The primary endpoint was self-reported pain using a visual analogue scale.

Harada 2009 compared 2 mg of dienogest daily with 300 µg of buserelin acetate (intranasally) daily in 271 women with confirmed endometriosis. The primary endpoint was self-reported pain.

Telimaa 1987b compared three groups of participants with mild to moderate endometriosis. They were randomised to either 100 mg medroxprogesterone once daily, 200 mg danazol three times daily or placebo for six months. Participants received identical packets of tablets so that each group took the same number of tablets daily as the active medroxyprogesterone or active danazol group. Twenty-seven per cent of participants did receive a surgical co-intervention at the study entry point but as they were evenly distributed in all three groups they were still included in the review. Change in the American Fertility Score and four-point verbal pain scores at the end of treatment were the relevant endpoint.

No other studies comparing progestagens with surgical therapy were identified.

Anti-progestagens

We identified no placebo controlled trial or no therapy trials comparing the anti-progestagen gestrinone. In addition, we identified no studies comparing gestrinone to any progestagen.

We identified two studies that compared gestrinone with danazol (Bromham 1995; Fedele 1989). Fedele 1989 reported on 39 infertile women with laparoscopically confirmed endometriosis. Patients received either 2.5 mg gestrinone twice weekly or 600 gm danazol per day. If amenorrhoea was not achieved, danazol was increased to 800 mg per day and gestrinone was increased to three times per week. The prevalence of pain symptoms as well as the change in the American Fertility Score at laparoscopy following treatment were considered the relevant endpoints. Bromham 1995 was a larger study, comparing 269 women who received either 2.5 mg gestrinone twice weekly or 200 mg danazol twice daily. American Fertility Scores at the laparoscopy following treatment and pain scores during treatment were similar endpoints. In this study 69 women withdrew during treatment.

We identified one multi-centre study (GISG 1996) comparing 2.5 mg gestrinone twice weekly with 3.75 mg leuprolin depot intramuscular monthly. Both groups also received a placebo pill or injection depending on their allocation. A change in severity of symptoms was measured by a 100 mm visual analogue score and a 0 to 3 point verbal rating scale.

One small study (Hornstein 1990) compared two doses of gestrinone, 1.25 mg versus 2.5 mg twice weekly. A total of six participants in each arm were assessed for a change in the Revised American Fertility Society Score of endometriosis as well as symptom scores.

Excluded studies

We excluded 13 studies from this Cochrane Review update (Cosson 2002; Dawood 1997; Harrison 2000; Mettler 1987; Nieto 1996; Noble 1980; Regidor 2001; Telimaa 1987a; Thomas 1987a; Vercellini 2005; Walch 2009; Worthington 1993; Yang 2006).

Risk of bias in included studies

Refer to the 'Risk of bias' tables and Figure 1 and Figure 2.

Allocation

Eight studies (Bergvist 2001; Bromham 1995; GISG 1996; Harada 2009; Hornstein 1990; Overton 1994; Schlaff 2006; Strowitzki 2010) included allocation concealment in their study design. In four studies (Razzi 2007; Telimaa 1987b; Vercellini 1996; Vercellini 2002) it was unclear whether allocation concealment was performed. The remaining trial failed to demonstrate allocation concealment in the study design (Fedele 1989).

Blinding

Six studies (Bergvist 2001; Bromham 1995; GISG 1996; Harada 2009; Schlaff 2006) included blinding in their study design. In four studies (Razzi 2007; Telimaa 1987b; Vercellini 1996; Vercellini 2002) it was unclear if blinding occurred. The remaining trials did not use blinding in their study design (Fedele 1989; Strowitzki 2010).

Incomplete outcome data

In three trials (Bergvist 2001; Schlaff 2006; Vercellini 2002) it was not possible to analyse the outcome data as they were in graphic or tabular form only. In the prior Cochrane review, the authors had successfully reported (with the exception of Vercellini 1996) all outcome data by contacting the appropriate authors.

Three studies reported large losses to follow-up. In Bromham 1995, 124 out of 265 did not complete the trial: five conceived before treatment, 69 withdrew during treatment and 50 were lost during the 12 months of follow-up. Similarly in Overton 1994, five patients were excluded post-randomisation (four conceived) and 23 were lost to follow-up out of a total of 62 patients. Finally, in Schlaff 2006 84 out of 247 did not complete the trial. Losses were equally distributed between groups in all three studies. All patients appear to have been followed up in the trial conducted by Razzi 2007 and the remaining trials provided numbers and reasons for losses (Harada 2009; Strowitzki 2010).

Selective reporting

All of the studies reported on a priori outcomes which had been stated in the methods section of the studies with the exception of Strowitzki 2010 who did not report on individual symptoms for the Biberglu and Behrman scores, which had been reported as an outcome in the trial methodology. The original protocols for each study were not accessed.

Other potential sources of bias

The authors are not aware of any other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Progestagen compared to placebo for pain associated with endometriosis; **Summary of findings 2** Depot progestagen compared to other treatment for pain associated with endometriosis; **Summary of findings 3** Oral progestagens versus other treatment for pain associated with endometriosis; **Summary of findings 4** Anti-progestagen compared to other treatment for pain associated with endometriosis

1. Progestagens versus no treatment or placebo

We did not identify any studies that compared progestagens with no treatment. Two trials compared a progestagen with placebo (Overton 1994; Telimaa 1987b).

Efficacy

Overton 1994 compared two doses of dydrogesterone (40 mg and 60 mg) with placebo given during the luteal phase. In this trial there was no significant improvement in objective efficacy (AFS scores) at six months with dydrogesterone (40 mg and 60 mg) compared to placebo (OR 0.53, 95% CI 0.14 to 1.94, not significant (NS)). Nor were any differences observed in the change in pain score at 12 months of follow-up with dydrogesterone compared to placebo (OR 0.80, 95% CI 0.27 to 2.37; NS). Wide confidence intervals were noted and the data should be interpreted with caution.

Telimaa 1987b reported on a trial of 51 participants of continuous progestin therapy (medroxprogesterone acetate) compared with placebo. When compared to placebo, medroxyprogesterone was more effective at the end of six months of treatment (Figure 3)

and 12 months follow-up (Figure 4): reduction of both pelvic pain (end of treatment MD -1.3, 95% CI -1.63 to -0.97; P < 0.00001; 12 month follow-up MD -0.85, 95% CI -1.19 to -0.51; P < 0.00001) and the sum of all symptoms (end of treatment MD -5.20, 95% CI -6.8 to -3.6; P < 0.00001; 12 months follow-up MD -7.0, 95% CI -8.61 to -5.39, P < 0.00001). There was however no objective improvement in AFS scores at 12 months of follow-up (MD -0.58, 95% CI -1.41 to 0.25; P = 0.17). The laparoscopy was performed six months after the completion of treatment and even though there was no objective improvement at that time the participants in the medroxyprogesterone arm still had an improvement in their subjective scores, questioning the assumption that it is the endometriotic implants that actually cause the pain associated with endometriosis.

Figure 3. Forest plot of comparison: 1 Progestagen versus placebo, outcome: 1.3 Patient assessed efficacy, 4 point verbal rating scale at end of treatment (6 months).

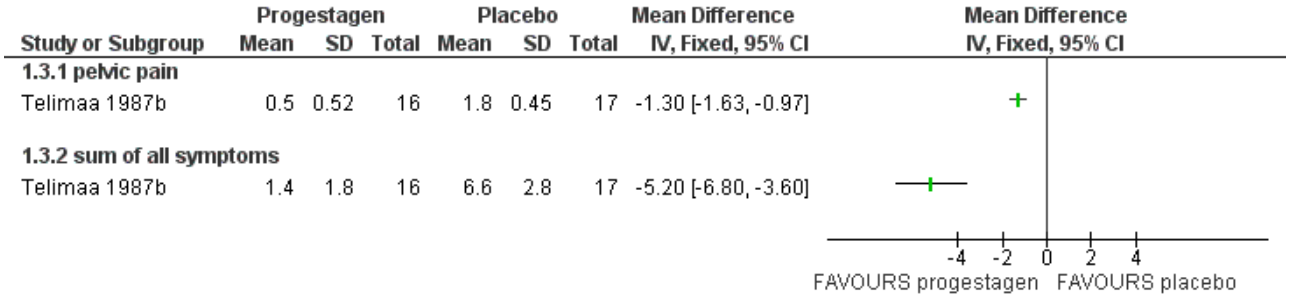
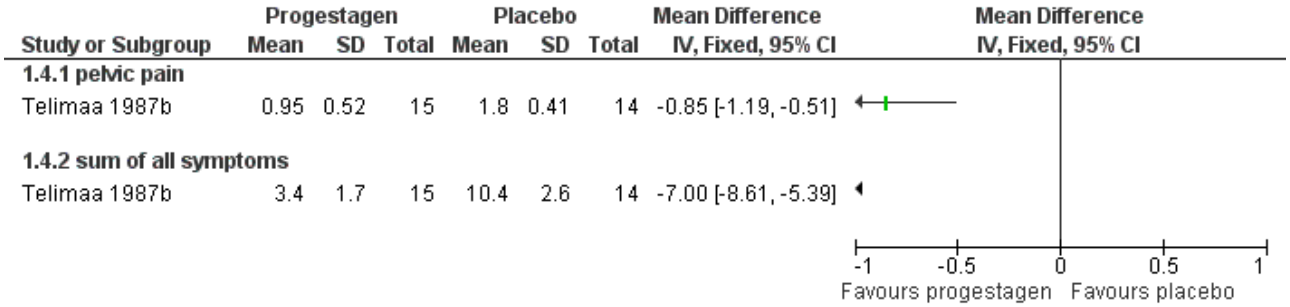


Figure 4. Forest plot of comparison: 1 Progestagen versus placebo, outcome: 1.4 Patient assessed efficacy, 4 point verbal rating scale at end of follow-up (12 months).



Adverse effects

Severe headaches and cycle irregularity resulted in five women withdrawing from the treatment during the active treatment phase (Overton 1994). Refer to Figure 5 and Figure 6.

Figure 5. Forest plot of comparison: 1 Progestagen versus placebo, outcome: 1.5 Change in pain score at 12 months follow-up (Improvement).

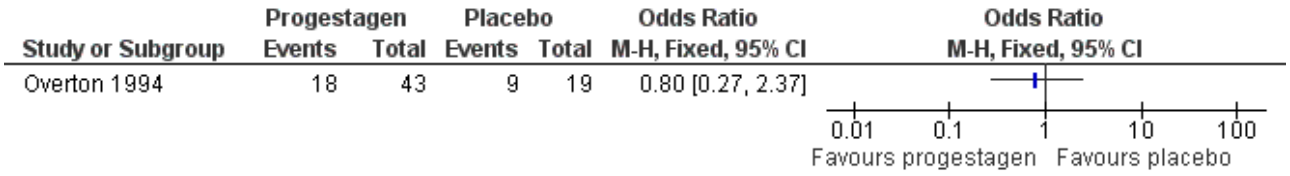
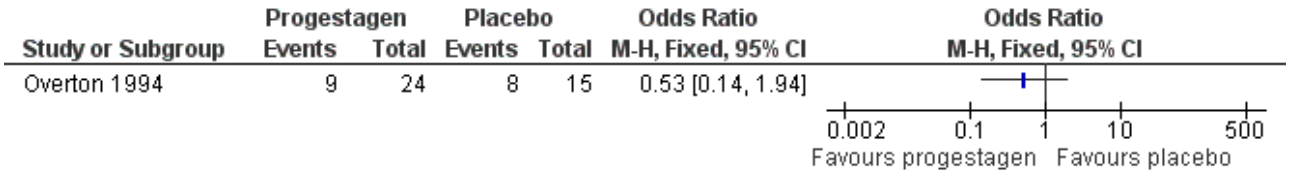
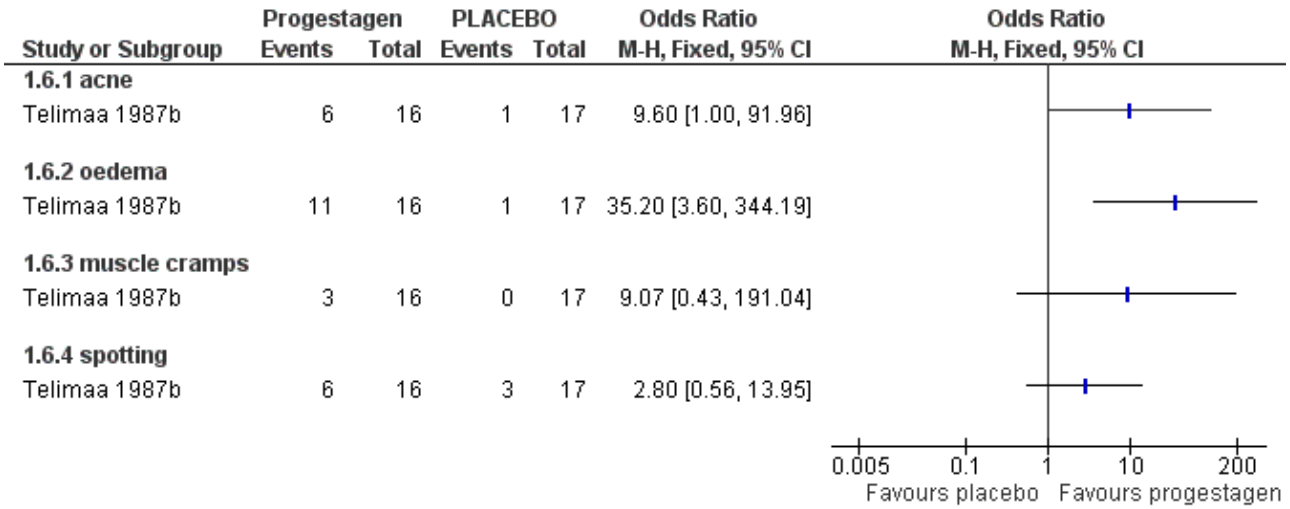


Figure 6. Forest plot of comparison: 1 Progestagen versus placebo, outcome: 1.2 AFS score (improved or remission).



There were significantly more cases of acne and oedema reported in the medroxprogesterone group than the placebo group (Telimaa 1987b). Refer to Figure 7 for details.

Figure 7. Forest plot of comparison: 1 Progestagen versus placebo, outcome: 1.6 Side effects.



2. Depot progestagens versus other treatment

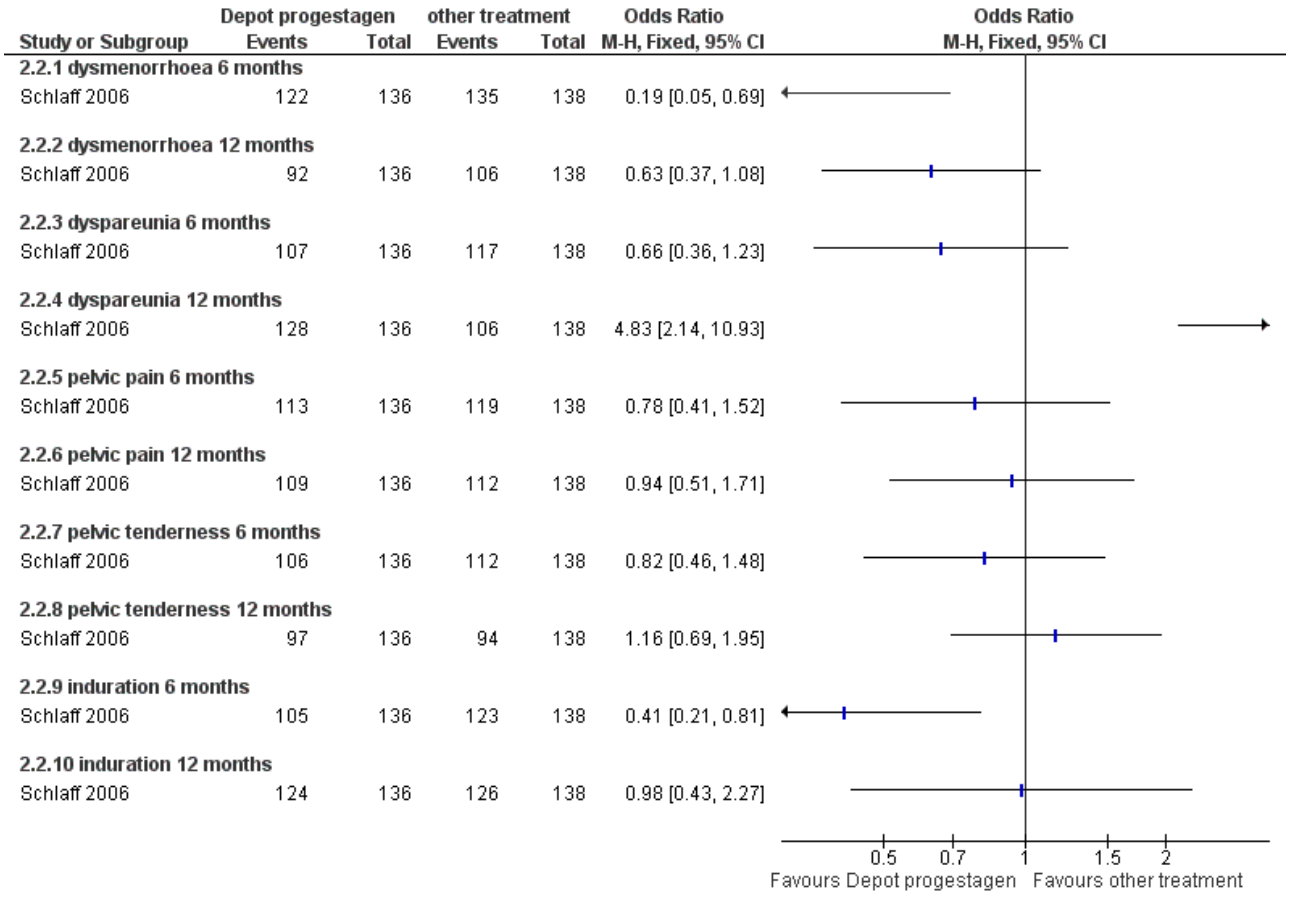
Two trials reported on the use of depot progestagens compared with other treatments (Schlaff 2006; Vercellini 1996).

Efficacy

Vercellini 1996 compared depot medroxyprogesterone acetate with a low dose oral contraceptive pill and 50 mg danazol. A significant reduction was observed in all symptom scores for both the visual analogue score and verbal rating scale in both study groups. The only difference was that dysmenorrhoea was improved in the progesterone only arm at 12 months follow-up (refer to Analysis 2.1).

Schlaff 2006 compared the efficacy of subcutaneous depot medroxyprogesterone acetate (DMPA) with leuprolide acetate. Symptoms of dysmenorrhoea were significantly reduced in the DMPA group at six months compared with the leuprolide acetate group (OR 0.19, 95% CI 0.05 to 0.69; P = 0.01) but this effect was not continued at the 12 months follow-up (OR 0.63, 95% CI 0.37 to 1.08). There was evidence of significantly fewer reports of induration at six months in the DMPA group compared with the leuprolide group (OR 0.41, 95% CI 0.21 to 0.81; P = 0.01). There were no differences between groups at 12 months follow-up. There was no evidence of a difference between groups for dyspareunia at six months. At 12 months significantly fewer women in the leuprolide group appeared to report dyspareunia (OR 4.83, 95% CI 2.14 to 10.93; P = 0.0002). There was no evidence of a difference between groups at six and 12 months for pelvic pain or pelvic tenderness. Refer to Figure 8.

Figure 8. Forest plot of comparison: 2 Depot progestagen versus other treatment, outcome: 2.2 Improvement in symptoms.



Adverse effects

Patients receiving depot progestagens had significantly more injection site reactions (OR 20.64, 95% CI 1.19 to 358.23; P = 0.04) than with other treatments. They also experienced more bloating (OR 4.39, 95% CI 1.71 to 11.30; P = 0.002), intermenstrual bleeding (OR 20.56, 95% CI 6.44 to 65.56; P < 0.00001), weight gain (OR 2.58, 95% CI 1.03 to 6.46; P = 0.04), amenorrhoea (OR 21.18, 95% CI 1.18 to 380.9; P = 0.04), and nausea (OR 3.86, 95% CI 1.12, 13.26; P = 0.03) compared with other treatments. Refer to Figure 9 . Although the number of hot flushes reported was significantly lower in the progestagen group (OR 0.30, 95% CI 0.11 to 0.83; P = 0.02), heterogeneity was high at I^2 = 66%. This was probably due to differences in the administration and timing of the depot injections (refer to Characteristics of included studies).

Figure 9. Forest plot of comparison: 2 Depot progestagen versus other treatment, outcome: 2.3 Side effects.

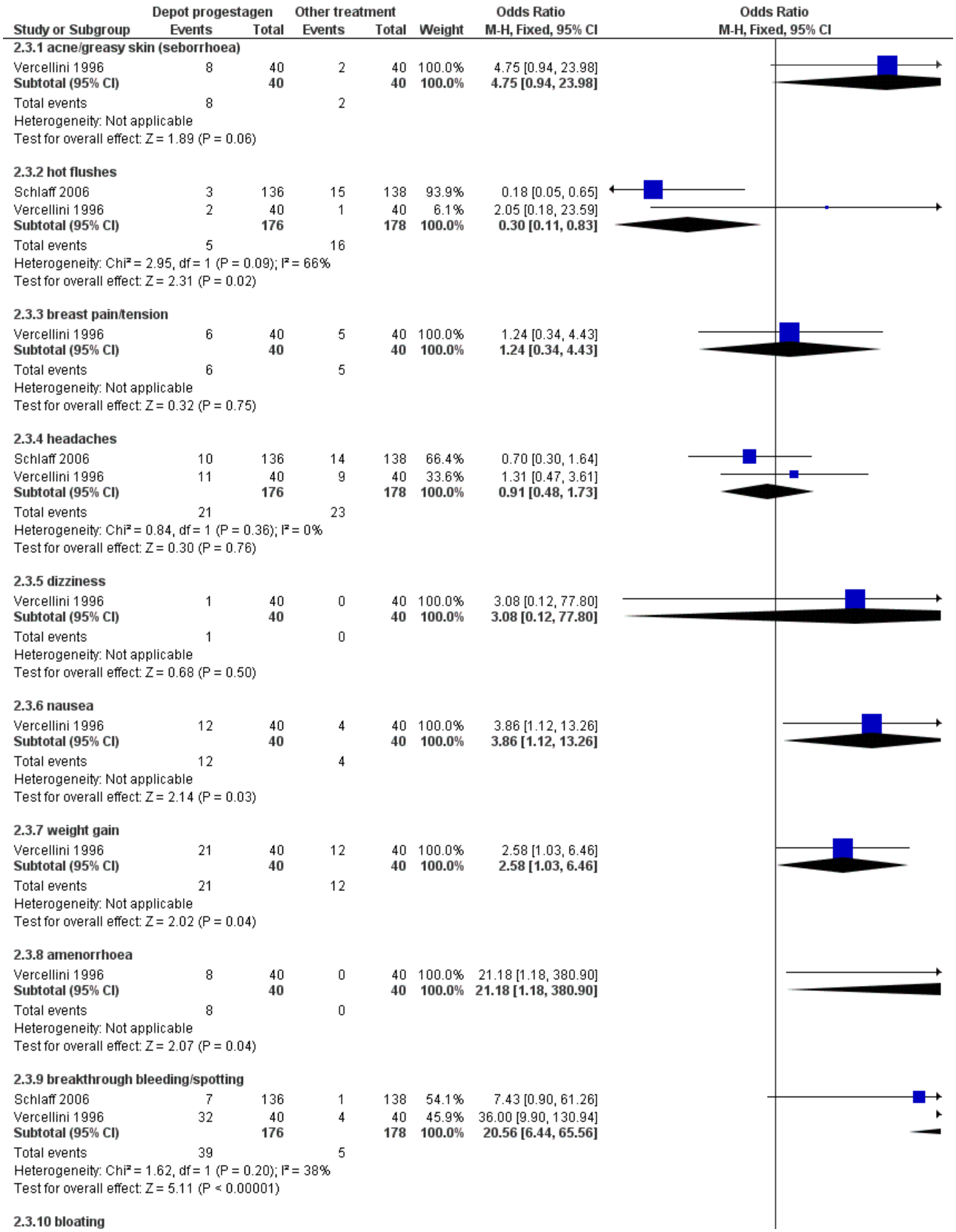
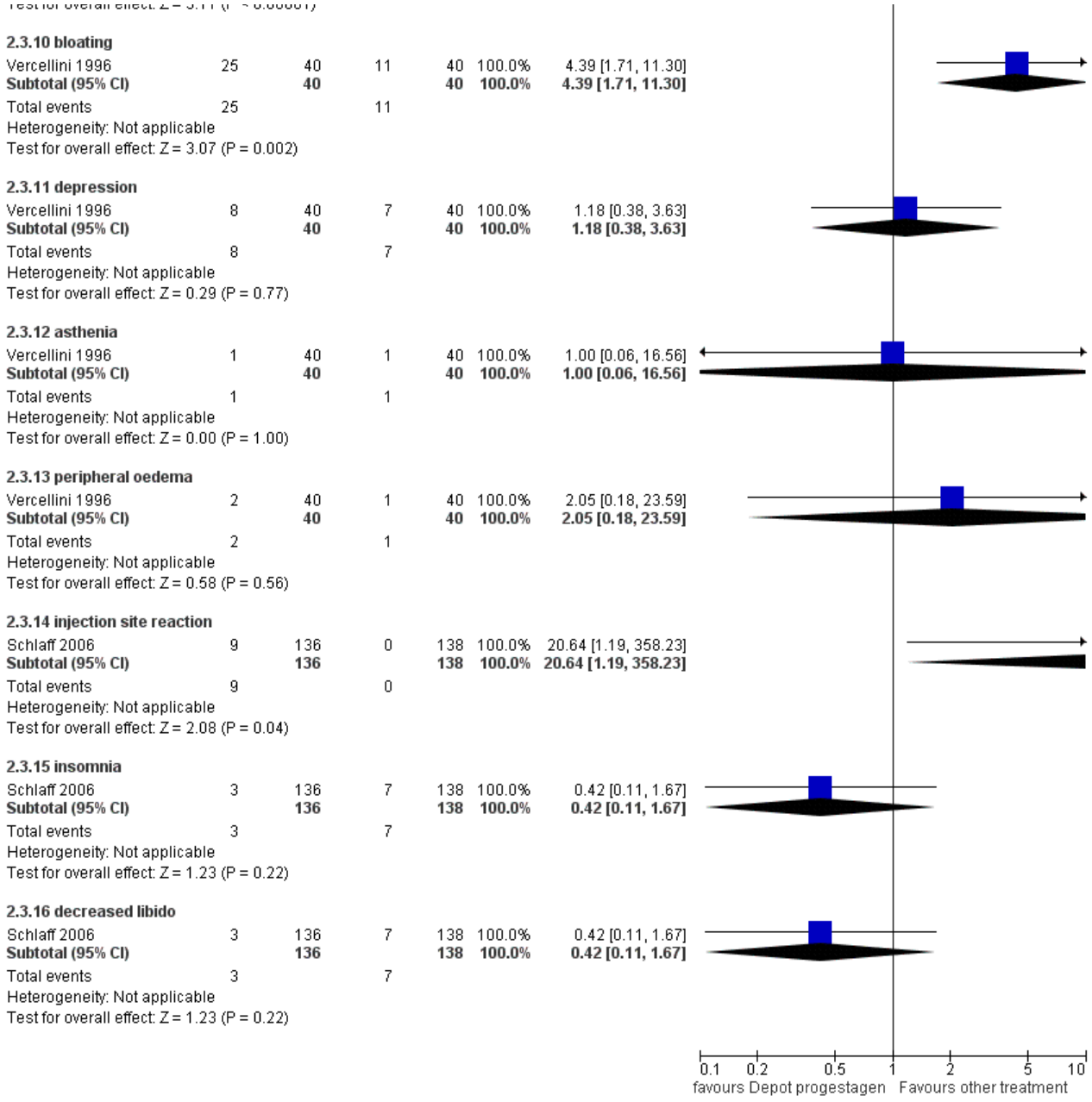


Figure 9. (Continued)



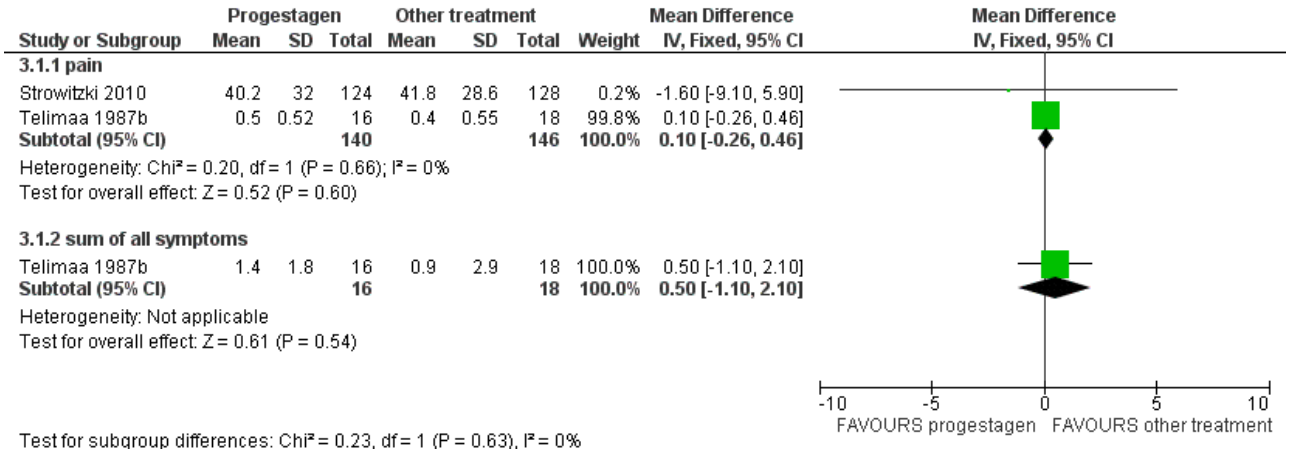
3. Oral progestagens versus other treatment

We identified six trials that had compared oral progestagens with other treatment (Bergvist 2001; Harada 2009; Razzi 2007; Strowitzki 2010; Telimaa 1987b; Vercellini 2002).

Efficacy

Telimaa 1987b compared oral medroxyprogesterone with danazol, and Strowitzki 2010 compared dienogest with a GnRH antagonist. In comparison to other treatments, there was no significant difference in self-reported pain (MD 0.10, 95% CI -0.26 to 0.46; NS) at six months (Figure 10) but at 12 months of follow-up medroxyprogesterone was more effective than danazol in subjective reduction of the sum of all symptoms (MD -3.4, 95% CI -4.83 to -1.97; P < 0.00001). Vercellini 2002 compared cytoproterone acetate with a low dose oral contraceptive pill. A substantial decrease was observed in all symptom scores on the visual analogue and verbal rating scores in both study groups but between group differences were not significant at six months of treatment (refer to Analysis 3.8; Analysis 3.9).

Figure 10. Forest plot of comparison: 3 Oral progestagens versus other treatment, outcome: 3.1 Patient assessed efficacy (6 months).

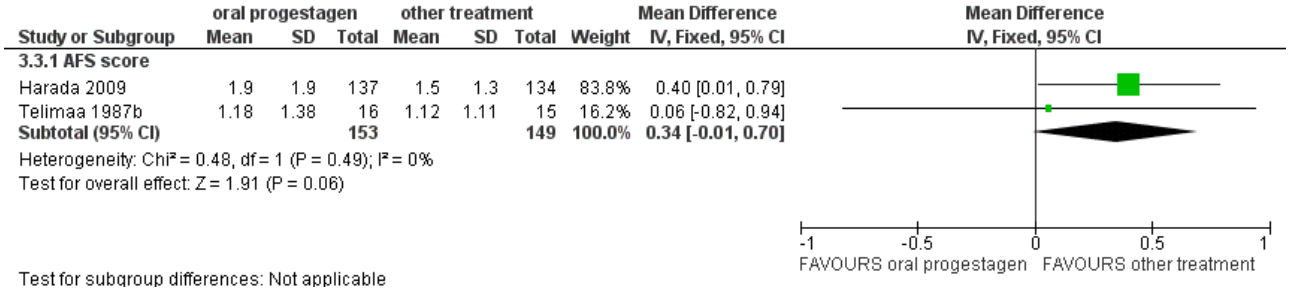


Bergvist 2001 compared the efficacy of medroxprogesterone acetate (MPA) and nafarelin. Although there was a significant reduction in bleeding, dysmenorrhoea, dyspareunia and pelvic pain in the total study group, there was no difference demonstrated between groups at six months of treatment or at 12 months of follow-up. There was no evidence of a statistically significant difference between the treatment groups for development of bleeding, pain symptoms or induration in the Total Endometriosis Severity Profile. Twelve of the MPA and six of the nafarelin group did not complete treatment. Data could not be included in the meta-analysis as it was presented as mean ranks and not raw scores.

Both desogestrel and the oral contraceptive showed significant decreases in self-reported pain compared to baseline (P < 0.001). After six months, the mean VAS score for desogestrel alone was 2.5 and for the oral contraceptive it was 2.3. There was no statistical comparison between groups. The authors reported on breakthrough bleeding in 4/20 patients randomised to desogestrel and increased body weight in 3/20 randomised to oral contraceptive. No other details were provided (Razzi 2007) (Analysis 3.9; Analysis 3.10).

Two studies reported no evidence of differences in objective efficacy (AFS score) between the two groups (MD 0.34, 95% CI -0.01 to 0.70; P = 0.06). Refer to Figure 11.

Figure 11. Forest plot of comparison: 3 Oral progestagens versus other treatment, outcome: 3.3 Objective efficacy at end of follow-up (12 months).



Adverse effects

Sleep disorder (OR 0.19, 95% CI 0.04 to 0.90; P = 0.04) and hot flushes (OR 0.49, 95% CI 0.31 to 0.76; P = 0.002) were more often reported in other treatments compared to oral progestagens. Significant heterogeneity was identified for the outcome of hot flushes (I^2 = 65%). Amenorrhoea (OR 4.95, 95% CI 2.88 to 8.52; P < 0.00001) and bleeding (OR 4.69, 95% CI 2.47 to 8.90; P < 0.00001) were reported more frequently in the oral progestagen group.

4. Anti-progestagens versus other treatment

Gestrinone was the only anti-progestagen used in the included trials. There were no RCTs of gestrinone compared with no treatment or placebo.

Efficacy

Two studies compared the efficacy of gestrinone with danazol (Bromham 1995; Fedele 1989). There appeared to be no difference in both subjective and objective measurements of pain between these two groups. For dysmenorrhoea the OR was 0.72 (95% CI 0.39 to 1.33; P = 0.30). Refer to Figure 12. Similarly, for objective assessment of the revised American Fertility Society (rAFS) assessment the MD was 1.40 (95% CI -6.76 to 9.56; P = 0.74). Refer to Figure 13

Figure 12. Forest plot of comparison: 4 Anti-progestagen versus other treatment, outcome: 4.1 Patient assessed efficacy at end of treatment (6 months).

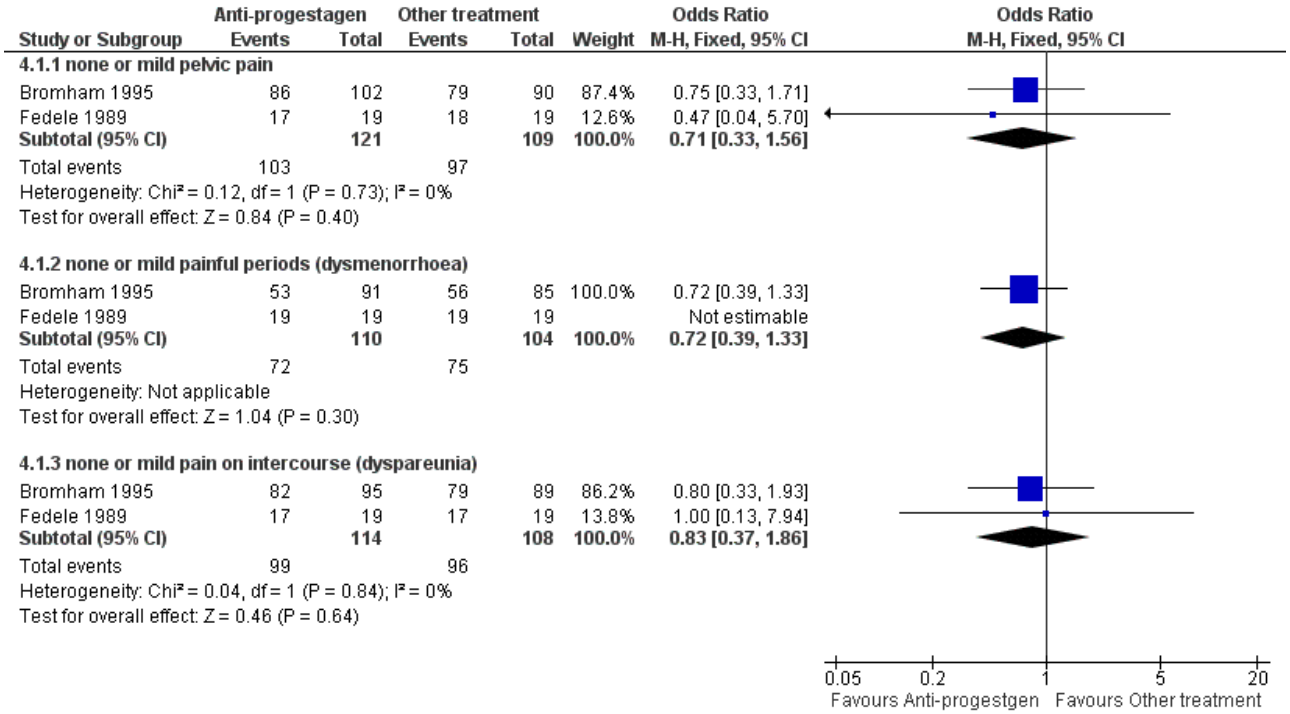
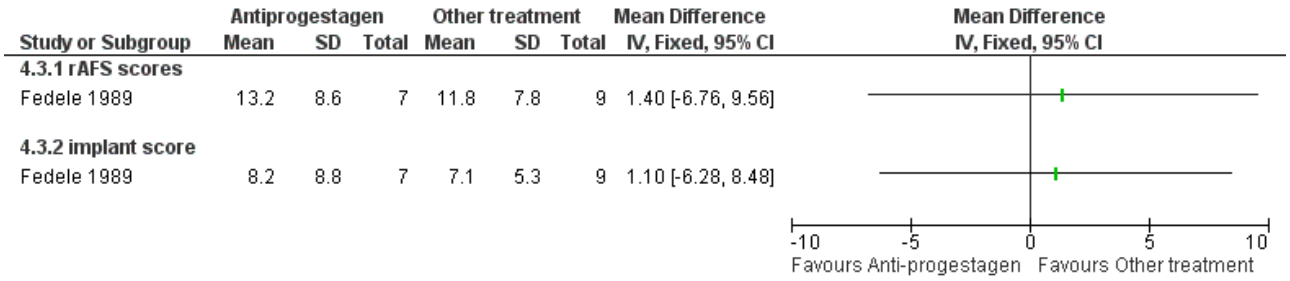


Figure 13. Forest plot of comparison: 4 Anti-progestagen versus other treatment, outcome: 4.3 Objective assessment of efficacy at end of treatment (6 months).



One study compared gestrinone with the GnRH analogue leuprolin IM (GISG 1996). There was evidence of a significant benefit in the reduction of dysmenorrhoea at six months (refer to Figure 14) for leuprolin (MD 0.82, 95% CI 0.15 to 1.49; P = 0.02); however at 12 months the advantage was with gestrinone (MD -3.0, 95% CI -4.79 to -1.21). Refer to Figure 15.

Figure 14. Forest plot of comparison: 4 Anti-progestagen versus other treatment, outcome: 4.4 Patient assessed efficacy at end of treatment (6 months).

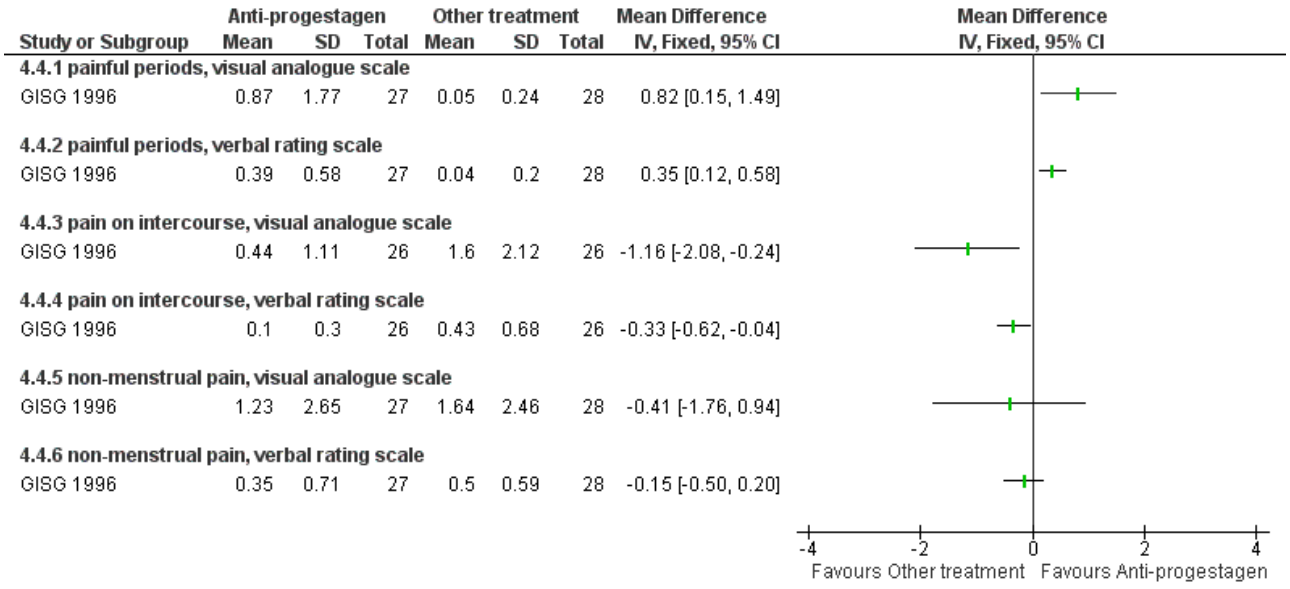
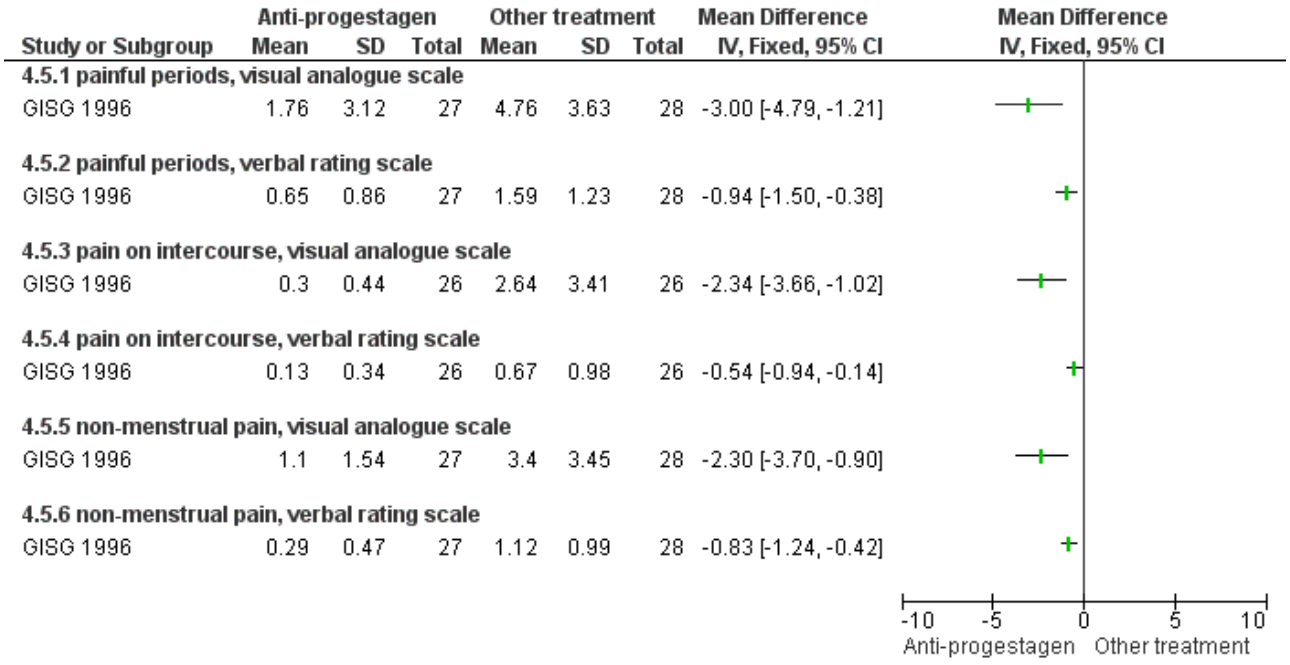


Figure 15. Forest plot of comparison: 4 Anti-progestagen versus other treatment, outcome: 4.5 Patient assessed efficacy at end of follow-up (12 months).



Adverse effects

Decreased breast size (OR 0.62, 95% CI 0.39 to 0.98; P = 0.04), muscle cramps (OR 0.48, 95% CI 0.30 to 0.77; P = 0.002), hot flushes (OR 0.65, 95% CI 0.42 to 0.99; P = 0.04), amenorrhoea (OR 0.04, 95% CI 0.01 to 0.38; P = 0.004), intermenstrual bleeding (OR 22.92, 95% CI 2.64 to 198.66; P = 0.004) and hunger (OR 0.59, 95% CI 0.36 to 0.97; P = 0.04) were more common in the other treatment group.

Hirsutism and seborrhoea (greasy skin) were more common in the anti-progestagen group (OR 2.63, 95% CI 1.60 to 4.32; P = 0.0001 and OR 2.74, 95% CI 1.69 to 4.46; P < 0.0001 respectively). Hirsutism had significant heterogeneity of I^2 = 68%, and also hot flushes with I^2 =78%. This is likely to be secondary to clinical heterogeneity, that is variation in study location and patient population.

5. Gestrinone versus gestrinone

Hornstein 1990 compared two doses of gestrinone. No difference in efficacy was noted in rAFS score, adverse effects or subjective improvement in pain between the two doses. This was, however, a very small study of only 12 patients.

D I S C U S S I O N

Summary of main results

Of the two trials that compared oral progestagens with placebo, only one identified a benefit for reduction of symptoms in favour of the progestagen (medroxyprogesterone). The remaining trial found no evidence of a difference between progestagen and the placebo group. Progestagens were associated with increased cases of adverse effects that included acne, oedema, headaches and cycle irregularity.

There was no evidence to suggest a benefit in symptoms for depot or oral administration of progestagens compared with other medical treatments. The progestagen groups experienced significantly more cases of adverse effects compared with other medical treatments.

There was no evidence to suggest a benefit in symptom reduction for anti-progestagens when compared with danazol; and a GnRH analogue was found to be superior to an anti-progestagen in one trial.

The 'Summary of findings' table illustrates the summary of the main outcomes.

Overall completeness and applicability of evidence

There are limited studies for each comparison and as such the applicability of the data is limited.

Quality of the evidence

There were 13 trials, including 1551 women. Randomisation and allocation concealment were adequately described in only six of the 13 trials. The quality of the trials was somewhat limited by a lack of blinding; only five trials reported on blinding, and who was blinded, four trials were open label and the remainder lacked clarity. Attrition was generally well described. The majority of the studies reported on a priori outcomes although the original protocols had not been viewed by the review authors.

Potential biases in the review process

The main bias remains the issue of multiple comparisons and small number of trials, making extrapolation difficult. There was a lack of consistency in the outcome measures used, which leads to difficulties in combining data in a suitable meta-analysis and thus makes it difficult to draw clinically relevant conclusions.

Agreements and disagreements with other studies or reviews

The additional studies have indicated that the effectiveness of progestagens and anti-progestagens is inconclusive at the current time. The benefits and harms observed are often limited to single trials and should be interpreted with caution.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

Whilst continuous medroxyprogesterone appeared to be effective at reducing symptoms when compared to placebo, it also appeared to have more side effects than placebo. There was no evidence of a benefit of depot or oral progestagens over other treatment. There was no evidence of a benefit of anti-progestagens. Data should be interpreted with caution due to the limited number of trials and small sample sizes.

Implications for research

At the present time there is limited high quality research looking at proven treatments for endometriosis in comparison to progestagens and anti-progestagens. A study design that replicates previous work, particularly oral administration of progestagens, would be desirable to allow combining trials in a systematic way and increasing our numbers of patients treated. In addition, a study that specifically compares medical therapy (with either a progestagen or anti-progestagen alone) versus surgical therapy only would be helpful, particularly since some literature suggests that the endometriotic implants may not necessarily be the cause of the pain and surgery could be avoided.

We identified no trials comparing placebo with gestrinone, but such a trial is unlikely to occur.

In the design of future trials, care should be taken to not obscure any valuable data by including surgical treatment (or other confounders) at the time of diagnosis and entry into the study.

A C K N O W L E D G E M E N T S

The authors wish to acknowledge the support of the Menstrual Disorders and Subfertility Group.

REFERENCES

References to studies included in this review

Bergvist 2001 *{published data only}*

Bergqvist A, Thorell T. Changes in quality of life after hormonal treatment for endometriosis. *Acta Obstetricia et Gynecologica Scandinavica* 2001;**80**:628-37.

Bromham 1995 *{published and unpublished data}*

Bromham DR, Booker MW, Rose GL, Wardle PG, Newton JR. A multicentre comparative study of gestrinone and danazol in the treatment of endometriosis. *Journal of Obstetrics and Gynaecology* 1995;**15**:188-94.

Bromham DR, Booker MW, Rose GL, Wardle PG, Newton JR. Updating the clinical experience in endometriosis - the European perspective. *British Journal of Obstetrics and Gynaecology* 1995;**102 Suppl 12**:12-6.

Fedele 1989 *{published data only}*

Fedele L, Arcaini L, Bianchi S, Viezzoli T, Arcaini L, Candiani GB. Gestrinone versus danazol in the treatment of endometriosis. *Fertility and Sterility* 1989;**51**(5):781-5.

Fedele L, Bianchi S, Marchini M, Di Nola G. Histological impact of medical therapy-clinical implications. *British Journal of Obstetrics and Gynaecology* 1995;**102 Suppl 12**:8-11.

GISG 1996 *{published data only}*

The Gestrinone Italian Study Group. Gestrinone versus a gonadotropin releasing hormone agonist for the treatment of pelvic pain associated with endometriosis: a multicenter, randomised, double-blind study. *Fertility and Sterility* 1996;**66**:911-9.

Harada 2009 *{published data only}*

Harada T, Momoeda M, Taketani Y, Takeshi A, Fukunaga M, Hagino H, et al. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis - a randomized, double blind, multi-centre trial. *Fertility and Sterility* 2009;**91**(3):675-81.

Hornstein 1990 *{published data only}*

Hornstein MD, Glaeson RE, Barbieri RL. A randomised, double-blind prospective trial of two doses of gestrinone in the treatment of endometriosis. *Fertility and Sterility* 1990;**53**(2):237-41.

Overton 1994 *{published data only}*

Overton CE, Lindsay PC, Johal B. A randomised, double-blind, placebo controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosis. *Fertility and Sterility* 1994;**62**(4):701-7.

Razzi 2007 *{published data only}*

Razzi S, Luisi S, Ferretti C, Calonaci F, Gabbanini M, Mazzini M, et al. Use of progestogen only preparation containing desogestrel in the treatment of recurrent pelvic pain after conservative surgery for endometriosis. *European Journal of Obstetrics and Gynecology* 2007;**135**:188-90.

Schlaff 2006 *{published data only}*

Sclaff W, Carson S, Luciano A, Ross D, Bergvist A. Subcutaneous injection of depot medoxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis associated pain. *Fertility and Sterility* 2006;**85**(2):314-25.

Strowitzki 2010 *{published data only}*

Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24 week, randomized, multicentre, open-label trial. *Human Reproduction* 2010;**25**(3):633-41.

Telimaa 1987b *{published and unpublished data}*

Kauppila A, Telimaa S, Ronnberg L, Vuori J. Placebo controlled study on serum concentrations of CA-125 before and after treatment of endometriosis with danazol or high-dose medroxyprogesterone acetate alone or after surgery. *Fertility and Sterility* 1988;**49**(1):37-41.

Telimaa S. Danazol and medroxyprogesterone acetate inefficacious in the treatment of infertility in endometriosis. *Fertility and Sterility* 1988;**50**(6):872-5.

Telimaa S, Poulakka J, Ronnberg L, Kauppila A. Placebo controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis. *Gynecological Endocrinology* 1987;**1**:13-23.

Vercellini 1996 *{published data only}*

Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis. *American Journal of Obstetrics and Gynecology* 1996;**175**:396-401.

Vercellini 2002 *{published data only}*

Vercellini P, De Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani P. Cytoproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. *American Journal of Obstetrics and Gynecology* 2002;**77**(1):52-61.

References to studies excluded from this review

Cosson 2002 *{published data only}*

Cosson M, Querleu D, Donnez J, Madelenat P, Koninckx P, Audebert A, et al. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. *Fertility and Sterility* 2002;**77**(4):684-92.

Dawood 1997 *{published data only}*

Dawood MY, Obasiolu CW, Ramos J, Khan-Dawood FS. Clinical, endocrine and metabolic effects of two doses of gestrinone in treatment of pelvic endometriosis. *American Journal of Obstetrics and Gynecology* 1997;**176**:387-94.

Harrison 2000 *{published data only}*

Harrison R, Barry-Kinsella C. Efficacy of medroxyprogesterone treatment in infertile women with endometriosis: a prospective, randomized, placebo-controlled trial. *Fertility and Sterility* 2000;**74**(1):24-30.

Mettler 1987 *{published data only}*

Mettler L, Semm K. Three-step therapy of genital endometriosis in cases of human infertility with lynestrenol, danazol or gestrinone administration in the second step. In: JP Raynaud editor(s). Medical Management of Endometriosis. New York: Raven Press, 1984:233-47.

Nieto 1996 *{published data only}*

Nieto A, Tacuri C, Serra M, Keller J, Cortes-Prieto J. Long term follow-up of endometriosis after two different therapies (gestrinone and buserelin). *Clinical & Experimental Obstetrics and Gynecology* 1996;**23**(4):199-203.

Noble 1980 *{published data only}*

Noble AD, Letchworth AT. Medical treatment of endometriosis: a comparative trial. *Postgraduate Medical Journal* 1979;**55 Suppl 5**:37-9.

Noble AD, Letchworth AT. Treatment of endometriosis: a study of medical management. *British Journal of Obstetrics and Gynaecology* 1980;**87**:726-8.

Regidor 2001 *{published data only}*

Regidor P, Regidor M, Schmidt M, Ruwe B, Lubben Fortig P, Kienle E, et al. Prospective randomized study comparing the GnRH-agonist leuprorelin acetate and gestagen lyestrenol in the treatment of severe endometriosis. *Gynecological Endocrinology* 2001;**15**:202-9.

Strowitzki 2009 *{published data only}*

Strowitzki T, Seitz C, Marr J, Gerlinger C, Faustmann T. Efficacy of dienogest for the treatment of endometriosis: a 24 week, randomised, open label trial versus leuprolide acetate. Human Reproduction. 2009; Vol. 24 Suppl 1.

Telimaa 1987a *{published data only}*

Telimaa S, Kauppila A, Ronnberg L, Suikkari AM, Seppala M. Elevated serum levels of endometrial secretory protein PP14 in patients with advanced endometriosis. *American Journal of Obstetrics and Gynecology* 1989;**161**:866-71.

Telimaa S, Penttila I, Puolakka J, Ronnberg L, Kauppila A. Circulating lipid and lipoprotein concentrations during danazol and high-dose medroxyprogesterone acetate therapy of endometriosis. *Fertility and Sterility* 1989;**52**(1):31-5.

Thomas 1987a *{published data only}*

Thomas EJ, Cooke ID. Impact of gestrinone on the course of asymptomatic endometriosis. *British Medical Journal* 1987;**294**:272-4.

Vercellini 2005 *{published data only}*

Vercellini P, Pietropaolo G, De Giogi O, Pasin R, Chiodini A, Crosignani P. Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low dose norethindrone acetate. *Fertility and Sterility* 2005;**84**(5):1375-87.

Walch 2009 *{published data only}*

Walch K, Unfried G, Huber J, Kurz C, Van Trotsenburg M, Pernicka E, et al. Implanon versus medoxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis - a pilot study. *Contraception* 2009;**79**:29-34.

Worthington 1993 *{published data only}*

Worthington M, Irvine LM, Crook D. A randomised comparative study of the metabolic effects of two regimens of gestrinone in the treatment of endometriosis. *Fertility and Sterility* 1993;**59**(3):522-6.

Yang 2006 *{published data only}*

Yang D, Ma W, Qu F, Ma B. Comparative study of Yiweining and gestrinone for post-operational treatment of stage 3 endometriosis. *Chinese Journal of Integrative Medicine* 2006;**12**(3):218-20.

Additional references

Augoulea 2008

Augoulea A, Lambrinoudaki I, Christodoulakos G. Thoracic endometriosis syndrome. *Respiration* 2008;**75**(1):113-9.

Barlow 1993

Barlow DH, Glynn CJ. Endometriosis and pelvic pain. *Clinical Obstetrics and Gynaecology* 1993;**7**(4):775-89.

Davis 2007

Davis L, Kennedy SS, Moore J, Prentice A. Modern combined oral contraceptives for pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD001019.pub2]

Haney 1993

Haney AF. Endometriosis-associated infertility. *Baillieres Clinical Obstetrics and Gynaecology* 1993;**7**(4):791-12.

Kistner 1958

Kistner RW. The use of newer progestins in the treatment of endometriosis. *American Journal of Obstetrics and Gynecology* 1958;**75**:264-78.

Kistner 1959

Kistner RW. Treatment of endometriosis by inducing pseudo-pregnancy with ovarian hormones. *Fertility and Sterility* 1959;**10**:539-54.

Kruitwagen 1993

Kruitwagen RF. Menstruation as the pelvic aggressor. *Baillieres Clinical Obstetrics and Gynaecology* 1993;**7**(4):687-700.

Lancaster 1995

Lancaster JM, Prentice A, Smith SK. Successful medical treatment of sub-diagphragmatic endometriosis. *Journal of Obstetrics and Gynaecology* 1995;**15**:206-9.

Mathias 1996

Mathias SD, Kupperman M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health related quality of life, and economic correlates. *Obstetrics and Gynaecology* 1996;**87**:321-7.

McLaren 1996

McLaren J, Prentice A. New aspects of pathogenesis of endometriosis. *Current Obstetrics and Gynaecology* 1996;**6**:85-91.

Moghissi 1990

Moghissi KS. Pseudopregnancy induced by estrogen-progestagen or progestagens alone in the treatment of endometriosis. *Progress in Clinical and Biological Research* 1990;**323**:221-32.

Prentice 1996

Prentice A, Ingamells S. Endometriosis and Infertility. *Journal of the British Fertility Society* 1996;**1**:51-5.

Rodgers 2008

Rodgers AK, Falcone T. Treatment strategies for endometriosis. *Expert Opinion on Pharmacotherapy* 2008;**9**(2):243-55.

Spitz 2003

Spitz IM. Progesterone antagonists and progesterone receptor modulators: an overview. *Steroids* 2003;**68**(10-13):981-93.

Wheeler 1989

Wheeler JM. Epidemiology of endometriosis-associated infertility. *Journal of Reproductive Medicine* 1989;**34**(1):41-6.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bergvist 2001

Methods	Randomised single centre Double dummy parallel study Method of randomisation not described
Participants	48 Swedish women 18-46 years Inclusion criteria: diagnosis of endometriosis by laparoscopy or laparotomy within 3 months regular menstruating and complaining of dysmenorrhoea, dyspareunia and/or pelvic pain Exclusion criteria: extensive adhesions, pelvic pain for other reasons, no surgery within the last 12 months with the exception of removal of an endometrioma, no use of laser or diathermy, steroid medication within 3 months or 1 month of diagnostic laparoscopy, previous use of any GnRH agonists, pregnant, breastfeeding or hysterectomy within 6 months prior to inclusion, use of concomitant contraceptive steroids, androgenic hormones, estrogens, progestagens, danazol,GnRh analogs, anxiolytics, cortizone and hypnotics,women with other concurrent disease either oncologic or psychiatric
Interventions	1. Nafarelin 200 µg intranasally (IN) BID and 'dummy' medroxyprogesterone tablets (23 women) 2. Medroxyprogesterone 15 mg PO BID and 'dummy' nafarelin nasal spray (25 women) Duration of treatment: 6 months
Outcomes	Pain scores using Biberoglu and Behrman scoring at 3, 6 and 12 months
Notes	18 withdrew from study Follow up: 6 months Unable to calculate means given data in current form

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described

Bergvist 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not detailed in paper
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double dummy, no details and no details of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Detail 18 women who withdrew, six from nafarelin group and 12 from MPA group - reasons not stated in paper
Selective reporting (reporting bias)	High risk	Main outcomes described, no details of side effects

Bromham 1995

Methods	Randomised double blind multi-centre study Method of randomisation not described Pharmaceutical company stated
Participants	269 British women aged 18-45 Inclusion criteria: endometriosis confirmed by laparoscopy or laparotomy. Exclusion criteria: those requiring surgical excision, serious systemic disease, those requiring long-term treatment, previous failure of danazol treatment, other hormonal treatment within 2 months, unwillingness to use mechanical contraception
Interventions	1. Gestrinone 2.5 mg twice weekly plus 'dummy' danazol for 6 months (132 women) 2. Danazol 200 mg bd plus 'dummy' gestrinone for 6 months (137 women) Duration of treatment: 6 months
Outcomes	AFS scores at laparoscopy following 6 months treatment Pain scores during treatment and 1 year follow-up Side effects Fertility
Notes	Repeat laparoscopy 23 days (median) after end of treatment Follow up: 12 months 5 women became pregnant before commencing treatment 69 withdrew during treatment 50 withdrew from follow-up phase

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Allocated at random'; no other details
Allocation concealment (selection bias)	Unclear risk	Unclear, no details in paper
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind' 'Double dummy'. Patients received two identical tablets. Authors state that patients were blinded but do not reveal who else was also blinded

Bromham 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Details provided of those women not included in the analysis and at what time point
Selective reporting (reporting bias)	Low risk	Include main outcomes and side effects

Fedele 1989

Methods	Open randomised trial No source of funding stated
Participants	39 Italian women aged 23-35 Inclusion criteria: infertility, laparoscopic diagnosis of endometriosis in preceding 3 months Exclusion criteria: bilateral tubal occlusion, severe dyspermia in partner, use of danazol or other sex steroids in preceding 6 months, severe systemic or endocrine disease
Interventions	1. Gestrinone 2.5 mg twice weekly (20 women) increasing to 3 times a week if no amenorrhoea by 1 month (7 of the 20) 2. Danazol 600 mg per day (19 women) increasing to 800 mg per day if no amenorrhoea by 1 month (2 of the 19) Duration of treatment: 6 months
Outcomes	rAFS scores at laparoscopy 1 month after end of treatment Pain scores during treatment and 18 month follow-up Plasma hormone levels before and during treatment Pregnancy rates post treatment Side effects
Notes	Only 7 gestrinone and 9 danazol patients had repeat laparoscopy Follow up: 12 months Losses to follow-up: 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'patients were randomly assigned'
Allocation concealment (selection bias)	High risk	No details provided
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for
Selective reporting (reporting bias)	High risk	All important outcomes reported with the exception of live birth

GISG 1996

Methods	Randomised double blind double dummy multi-centre trial Method of randomisation described Pharmaceutical company stated
Participants	55 Italian women aged 18-40 Inclusion criteria: chronic pelvic pain, laparoscopic diagnosis of endometriosis with no attempts at endometriosis reduction other than biopsy up to 3 months before study entry, no medical or surgical treatment for endometriosis between laparoscopy and study entry, not wanting pregnancies in the immediate future Exclusion criteria: treatment for endometriosis other than non steroidal anti inflammatory drugs in the previous 6 months, concomitant pelvic pain causing disorders, contraindications to the use of gestrinone or GnRH analogues, abnormal baseline bone density values, unwillingness to use barrier contraception
Interventions	1. Gestrinone 2.5 mg twice weekly plus placebo injections (27 women) 2. Intramuscular (IM) leuprolide acetate 3.75mg once a month plus placebo tablets (28 women) Duration of treatment: 6 months
Outcomes	Pain symptoms Bone mineral density Lipid profile
Notes	Follow up: 6 months 6 withdrawals during treatment period 7 lost to follow-up 8 pregnancies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'randomized' 'allocating consecutively numbered anonymous packages'
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing randomization codes'
Blinding (performance bias and detection bias) All outcomes	Low risk	'Double blind, double dummy'. Each patient received an active drug and a dummy placebo. Patients and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow up detailed, 6 withdrawals during treatment period 7 lost to follow-up
Selective reporting (reporting bias)	High risk	Did not include live births

Harada 2009

Methods	Randomised double blind, multi-centre trial
Participants	Japan (24 centres) N = 271

Harada 2009 *(Continued)*

	Inclusion: 20 years or older, regular menstrual cycles, endometriosis diagnosed by laparotomy, laparoscopy or imaging analysis, the presence of subjective symptoms during menstruation, the presence of subjective symptoms during non-menstruation, presence of objective findings Exclusion: undiagnosed genital bleeding, class 3 or more on Pap test within 3 months before enrolment, use of GnRH agonists, testosterone derivatives, hormonal therapy with progesterone and/or oestrogen, oestrogen antagonists, or aromatase inhibitors within 16 weeks before enrolment. Pregnant or nursing, history of severe adverse reaction or hypersensitivity to steroid hormone or GnRH agonists, past use of GnRH agonists with low BMD, having undergone surgery therapy or surgical examination for endometriosis within a menstrual cycle before the start of medication, use of drugs that could be expected to affect the release of sex hormones, a history or complication of thrombosis/embolism or depression, malignant tumour complication or findings suggestive of malignancy, complication of serious heart, liver, kidney, blood or endocrine disease, participating in another clinical trial in previous 4 months, deemed to be unsuitable
Interventions	Treated for 24 weeks with 2 mg dienogest daily PO (n = 137) versus 300 µg buserelin acetate IN TDS (n = 134)
Outcomes	Self-reported pain, QoL, BMD, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by permuted block
Allocation concealment (selection bias)	Low risk	' allocation sequence...was kept centrally...'
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, patients were blinded using a double dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawals given in paper
Selective reporting (reporting bias)	Low risk	A priori outcomes reported as per methods section. Protocol not accessed

Hornstein 1990

Methods	Randomised double blind trial Pharmaceutical company stated
Participants	12 American women Inclusion criteria: endometriosis (stage 2-3 disease according to rAFS classification) diagnosed on videotaped laparoscopy within previous 6 weeks Exclusion criteria: none specified
Interventions	1. Gestrinone 1.25 mg twice weekly (6 women) 2. Gestrinone 2.5 mg twice weekly (6 women)

Hornstein 1990 *(Continued)*

	Duration of treatment: 6 months
Outcomes	rAFS scores of endometriosis at laparoscopy following treatment Symptom scores during treatment and follow-up Side effects Bone densitometry Hormonal, lipoprotein, haematological and biochemical measurements
Notes	Second laparoscopy within 4 weeks of completing treatment Follow-up: 6 months Losses to follow-up: 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised trial
Allocation concealment (selection bias)	Low risk	A - Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 2
Selective reporting (reporting bias)	High risk	Not addressed live births

Overton 1994

Methods	Double blind randomised multi-centre study Randomisation method stated Pharmaceutical company stated
Participants	62 British women aged 21-42 years Inclusion criteria: minimal - mild endometriosis (AFS classification score 1-15, stage 1 or 2) diagnosed at laparoscopy within preceding 3 months, women with azoospermic partners who had had more than 12 cycles of unsuccessful donor insemination, women taking clomiphene citrate or cyclofenil for ovulation induction also included Exclusion criteria: women taking corticosteroids, hormones, danazol, or GnRH agonists in month before admission to the study
Interventions	1. 40 mg dydrogesterone for 12 days starting 2 days after LH surge 2. 60 mg dydrogesterone given as above 3. Placebo given as above. Duration of treatment: 6 months
Outcomes	Conception rates Change in AFS scores at laparoscopy following treatment Pain scores Bleeding

Overton 1994 *(Continued)*

Notes	Follow-up: 12 months Second laparoscopy within 3 months of completing treatment Exclusions post randomisation: 5 never treated, 1 refused, 4 conceived Losses to follow-up: 23

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'women were allocated randomly' 'using computer generated randomization lists'
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double blind, no details in paper
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions: 5 never treated, 1 refused, 13 conceived, 5 had unwanted side effects, 5 withdrew for miscellaneous/social reasons
Selective reporting (reporting bias)	High risk	No details of live birth

Razzi 2007

Methods	RCT
Participants	Italy n = 40 women with mild endometriosis (stage I-II) Age range 23 to 35 years Diagnosed by laparoscopy and clinical symptomology
Interventions	Desogestrel 75 µg per day (n = 20) versus ethinylestrdiol plus desogestrel (EE 20 µg + desogestrel 150 µg per day) Follow-up: 6 months
Outcomes	Pain score (VAS 0-10), serum glucose, cholesterol and triglycerides, side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomized' no other details
Allocation concealment (selection bias)	Unclear risk	Not stated

Razzi 2007 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear to have been followed up
Selective reporting (reporting bias)	Low risk	All a priori outcomes were reported on

Schlaff 2006

Methods	Randomised, evaluator blinded, multi-centre (7 sites) trial
Participants	274 Candian and North American pre-menopausal women aged 18-49. Mean age DMPA 29.2±6.3, Leuprolide 32.1±6.6 (P < 0.001) Inclusion criteria: endometriosis surgically diagnosed within 42 months and pain within 30 days of diagnostic laparoscopy or after 3 months following laparoscopy or laparotomy; Biberoglu & Behrman score ≥ 6 including at least 2 in symptoms of dysmenorrhoea, dyspareunia and pelvic pain; pain must persist more than 3 months Exclusion criteria: BMD at lumbar spine or hip < v1.0SD below mean for peak adult bone mass
Interventions	Depomedroxyprogesterone acetate 104 mg SC every 3 months (n = 136) versus leuprolide 11.25 mg IM every 3 months (n = 138) Treatment duration - 6 months
Outcomes	Pain scores during treatment at 12 months post treatment, BMD, adverse events, hyperoestrogenic symptoms, bleeding, and quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state 'randomised', no other details
Allocation concealment (selection bias)	Low risk	Centrally randomised by an independent investigator
Blinding (performance bias and detection bias) All outcomes	Low risk	Principle investigator and sub investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	DMPA drop out was 48/136 and leuprolide was 36/138, non-specific reasons given
Selective reporting (reporting bias)	Low risk	A priori outcomes presented as per methods section of paper. Protocol not accessed

Strowitzki 2010

Methods	Multi-centre, open label, randomised trial
Participants	Germany, Poland, Portugal, Spain and Austria (17 centres) n = 252 Inclusion: women aged 18-45 years, experiencing pain with histologically confirmed endometriosis stage I-IV. Laparoscopic diagnosis Exclusion: pregnancy or breast feeding, amenorrhoea within 3 months of screening, a primary need for surgical treatment, previous use of hormonal agents (GnRH agonists ≤, progestins/danazol ≤ 3 months or oral contraceptives ≤ 1 month), abnormal gynaecological examination or smear test result or risk factors for decreased bone mineral density
Interventions	Dienogest 2 mg daily PO (n = 124) versus leuprolide acetate 3.75 mg depot IM every 4 weeks (n = 128) Treatment for 24 weeks
Outcomes	Absolute change in pelvic pain using VAS (0-100); improvement in pain (VAS); responder rates, Biberoglu & Behrman (B&B) scores; QoL; adverse effects, BMD
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'randomization blocks'
Allocation concealment (selection bias)	Low risk	Randomisation done centrally
Blinding (performance bias and detection bias) All outcomes	High risk	'open label'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drops outs recorded and reasons given in text
Selective reporting (reporting bias)	High risk	Did not show data on individual symptoms for B&B scores

Telimaa 1987b

Methods	Double blind double dummy single centre study Randomisation method not clear
Participants	59 participants aged 26-38 with mild to moderate endometriosis No previous medical or surgical treatment No exclusion criteria specified 9 participants lost to follow-up
Interventions	Danazol 200 mg PO TDS

Telimaa 1987b *(Continued)*

	Medroxyprogesterone acetate 100 mg PO daily Placebo All medications taken for 180 days
Outcomes	Change in AFS scores Patient reported pain symptoms Side effects
Notes	27% of patients had electro-coagulation of implants at initial diagnostic laparoscopy 2nd look laparoscopy was performed 6 months after completion of treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors state 'randomised' but no other details
Allocation concealment (selection bias)	Unclear risk	No details in paper
Blinding (performance bias and detection bias) All outcomes	Unclear risk	State 'double blind' but no other details
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers of patients not completing study in placebo group does not add up correctly
Selective reporting (reporting bias)	Unclear risk	A priori outcomes reported but original protocol not sighted

Vercellini 1996

Methods	Open randomised trial No source of funding stated
Participants	80 Italian women aged 18-40 years Inclusion criteria: first diagnosis of endometriosis at laparoscopy with attempt at implant reduction other than biopsy in the previous 3 months, pelvic pain of greater than 6 months duration Exclusion criteria: treatment for endometriosis other than non-steroidal anti-inflammatory drugs in preceding 3 months, contraindications to taking estrogens, progestagens or danazol, a desire to conceive in the next 2 years
Interventions	1. Depot medroxyprogesterone acetate 150 mg every 90 days 2. Oral contraceptive pill (ethinyl estradiol 0.02 mg + desogestrel 0.15mg) plus 50 mg danazol daily for 21 days out of 28 Duration of treatment: 12 months
Outcomes	Pain scores Side effects Fasting cholesterol, HDL, LDL 17 beta estradiol (in medroxyprogesterone acetate group)
Notes	Follow-up: no post-treatment follow-up 11 withdrawals

Vercellini 1996 *(Continued)*

	1 lost to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'computer generated randomised sequence'
Allocation concealment (selection bias)	Low risk	'serially numbered, opaque, sealed envelopes'
Blinding (performance bias and detection bias) All outcomes	High risk	'open label', subjects not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 MDPA withdrew (3 for prolonged bleeding and 1 for persistent pain); seven in the oral contraceptive pill (OCP) + danazol (3 for persistent pain, two for bloating and weight gain, 2 for personal reasons)
Selective reporting (reporting bias)	Unclear risk	A priori outcomes reported but original protocol not sighted

Vercellini 2002

Methods	RCT
Participants	90 women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis Inclusion: 18-40 years, not desiring pregnancy, who had undergone conservative surgery at laparoscopy or laparotomy for stage I-IV symptomatic disease in the previous 12 months. Only included women with confirmed surgical eradication and who had recurrent pelvic pain for more than 6 months Exclusion: therapies other than non-steroidal anti-inflammatories
Interventions	6 months treatment Oral cyproterone acetate 12.5mg/d versus oral contraceptive - ethinyl estradiol 0.02 mg and desogestrel 0.15 mg
Outcomes	Biberoglu and Behrman scores and VAS for pain
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias)	High risk	No blinding - open label study

Vercellini 2002 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	6 in the cyproterone acetate group and 9 in the oral contraceptive group withdrew due to side effects (n = 9), treatment inefficacy (n = 4) or loss to follow-up (n = 2)
Selective reporting (reporting bias)	Unclear risk	Unclear

AFS: American Fertility Society
BD/ BID:Twice daily
BMD: Bone mineral density
DMPA: Depot medroxyprogesterone acetate
GnRH: Gonadotrophin releasing hormone
IM: Intramuscular
IN: Intranasal
MDPA/MPA:Medroxyprogesterone acetate
QoL: Quality of life
rAFS: revised American Fertility Society
SC: Subcutaneous
TDS:Three time daily
VAS:Visual analogue scale/score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cosson 2002	All patients received surgery immediately prior to medical therapy
Dawood 1997	Pain data not reported separately for the two groups. Relief of pain was not a primary endpoint
Harrison 2000	Relief of pain was not an outcome in this study
Mettler 1987	The "three step" therapy discussed in this study is a mixture of surgical and medical therapy
Nieto 1996	23/25 patients on gestrinone and 18/18 patients on danazol had surgery prior to medical treatment
Noble 1980	Comparison of danazol with oral contraceptive pill
Regidor 2001	All patients had received surgery immediately prior to medical therapy
Strowitzki 2009	This is a conference abstract that has been superseded by a full text paper which has been included in the review
Telimaa 1987a	Patients were recruited to the study following surgical treatment
Thomas 1987a	This study does not have relief of pain as an outcome measure; it concentrates on effects on fertility
Vercellini 2005	Patients had rectovaginal endometriosis only
Walch 2009	Comparison was between 2 progestagens
Worthington 1993	Relief of pain is not an outcome considered in this study
Yang 2006	The comparison group received a complementary therapy intervention

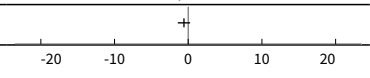
DATA AND ANALYSES

Comparison 1. Progestagen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 AFS score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 AFS score (improved or remission)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Patient assessed efficacy, 4 point verbal rating scale at end of treatment (6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 pelvic pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 sum of all symptoms	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Patient assessed efficacy, 4 point verbal rating scale at end of follow-up (12 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 pelvic pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 sum of all symptoms	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in pain score at 12 months follow-up (Improvement)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 acne	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 oedema	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 muscle cramps	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 spotting	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

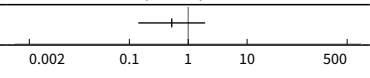
Analysis 1.1. Comparison 1 Progestagen versus placebo , Outcome 1 AFS score .

Study or subgroup	Progestagen N	Progestagen Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Telimaa 1987b	16	1.2 (1.4)	17	1.8 (1)		-0.58[-1.41,0.25]



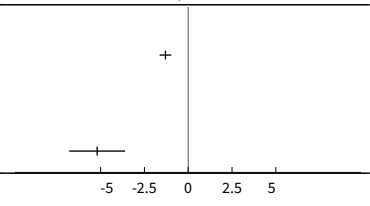
Analysis 1.2. Comparison 1 Progestagen versus placebo , Outcome 2 AFS score (improved or remission) .

Study or subgroup	Progestagen n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Overton 1994	9/24	8/15		0.53[0.14,1.94]



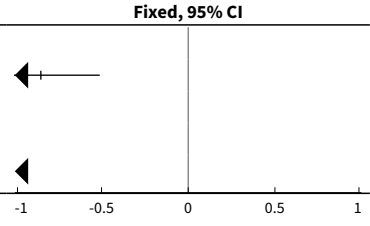
Analysis 1.3. Comparison 1 Progestagen versus placebo , Outcome 3 Patient assessed efficacy, 4 point verbal rating scale at end of treatment (6 months).

Study or subgroup	Progestagen N	Progestagen Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 pelvic pain						
Telimaa 1987b	16	0.5 (0.5)	17	1.8 (0.5)		-1.3[-1.63,-0.97]
1.3.2 sum of all symptoms						
Telimaa 1987b	16	1.4 (1.8)	17	6.6 (2.8)		-5.2[-6.8,-3.6]



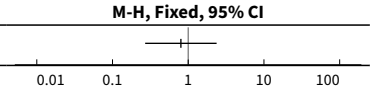
Analysis 1.4. Comparison 1 Progestagen versus placebo , Outcome 4 Patient assessed efficacy, 4 point verbal rating scale at end of follow-up (12 months).

Study or subgroup	Progestagen N	Progestagen Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.4.1 pelvic pain						
Telimaa 1987b	15	1 (0.5)	14	1.8 (0.4)		-0.85[-1.19,-0.51]
1.4.2 sum of all symptoms						
Telimaa 1987b	15	3.4 (1.7)	14	10.4 (2.6)		-7[-8.61,-5.39]



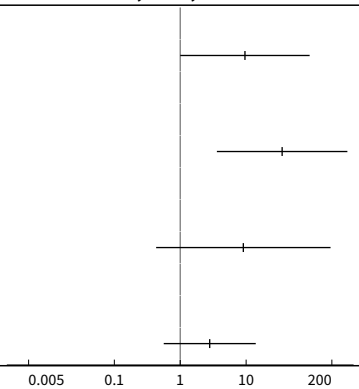
Analysis 1.5. Comparison 1 Progestagen versus placebo , Outcome 5 Change in pain score at 12 months follow-up (Improvement).

Study or subgroup	Progestagen n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Overton 1994	18/43	9/19		0.8[0.27,2.37]



Analysis 1.6. Comparison 1 Progestagen versus placebo , Outcome 6 Side effects.

Study or subgroup	Progestagen n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.6.1 acne				
Telimaa 1987b	6/16	1/17		9.6[1,91.96]
1.6.2 oedema				
Telimaa 1987b	11/16	1/17		35.2[3.6,344.19]
1.6.3 muscle cramps				
Telimaa 1987b	3/16	0/17		9.07[0.43,191.04]
1.6.4 spotting				
Telimaa 1987b	6/16	3/17		2.8[0.56,13.95]



Comparison 2. Depot progestagen versus other treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient assessed efficacy during and at end of treatment (6 and 12 months)			Other data	No numeric data
1.1 painful periods, visual analogue scale			Other data	No numeric data
1.2 painful periods, verbal rating scale			Other data	No numeric data
1.3 pain on intercourse, visual analogue scale			Other data	No numeric data
1.4 pain on intercourse, verbal rating scale			Other data	No numeric data
1.5 non-menstrual pain, visual analogue scale			Other data	No numeric data
1.6 non-menstrual pain, verbal rating scale			Other data	No numeric data
2 Improvement in symptoms	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 dysmenorrhoea 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 dysmenorrhoea 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 dyspareunia 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

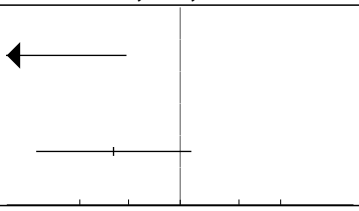
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.4 dyspareunia 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 pelvic pain 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 pelvic pain 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 pelvic tenderness 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 pelvic tenderness 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 induration 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 induration 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Side effects	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 acne/greasy skin (seborrhoea)	1	80	Odds Ratio (M-H, Fixed, 95% CI)	4.75 [0.94, 23.98]
3.2 hot flushes	2	354	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.11, 0.83]
3.3 breast pain/tension	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.34, 4.43]
3.4 headaches	2	354	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.48, 1.73]
3.5 dizziness	1	80	Odds Ratio (M-H, Fixed, 95% CI)	3.08 [0.12, 77.80]
3.6 nausea	1	80	Odds Ratio (M-H, Fixed, 95% CI)	3.86 [1.12, 13.26]
3.7 weight gain	1	80	Odds Ratio (M-H, Fixed, 95% CI)	2.58 [1.03, 6.46]
3.8 amenorrhoea	1	80	Odds Ratio (M-H, Fixed, 95% CI)	21.18 [1.18, 380.90]
3.9 breakthrough bleeding/spotting	2	354	Odds Ratio (M-H, Fixed, 95% CI)	20.56 [6.44, 65.56]
3.10 bloating	1	80	Odds Ratio (M-H, Fixed, 95% CI)	4.39 [1.71, 11.30]
3.11 depression	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.38, 3.63]
3.12 asthenia	1	80	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.56]
3.13 peripheral oedema	1	80	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.18, 23.59]
3.14 injection site reaction	1	274	Odds Ratio (M-H, Fixed, 95% CI)	20.64 [1.19, 358.23]
3.15 insomnia	1	274	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.11, 1.67]
3.16 decreased libido	1	274	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.11, 1.67]

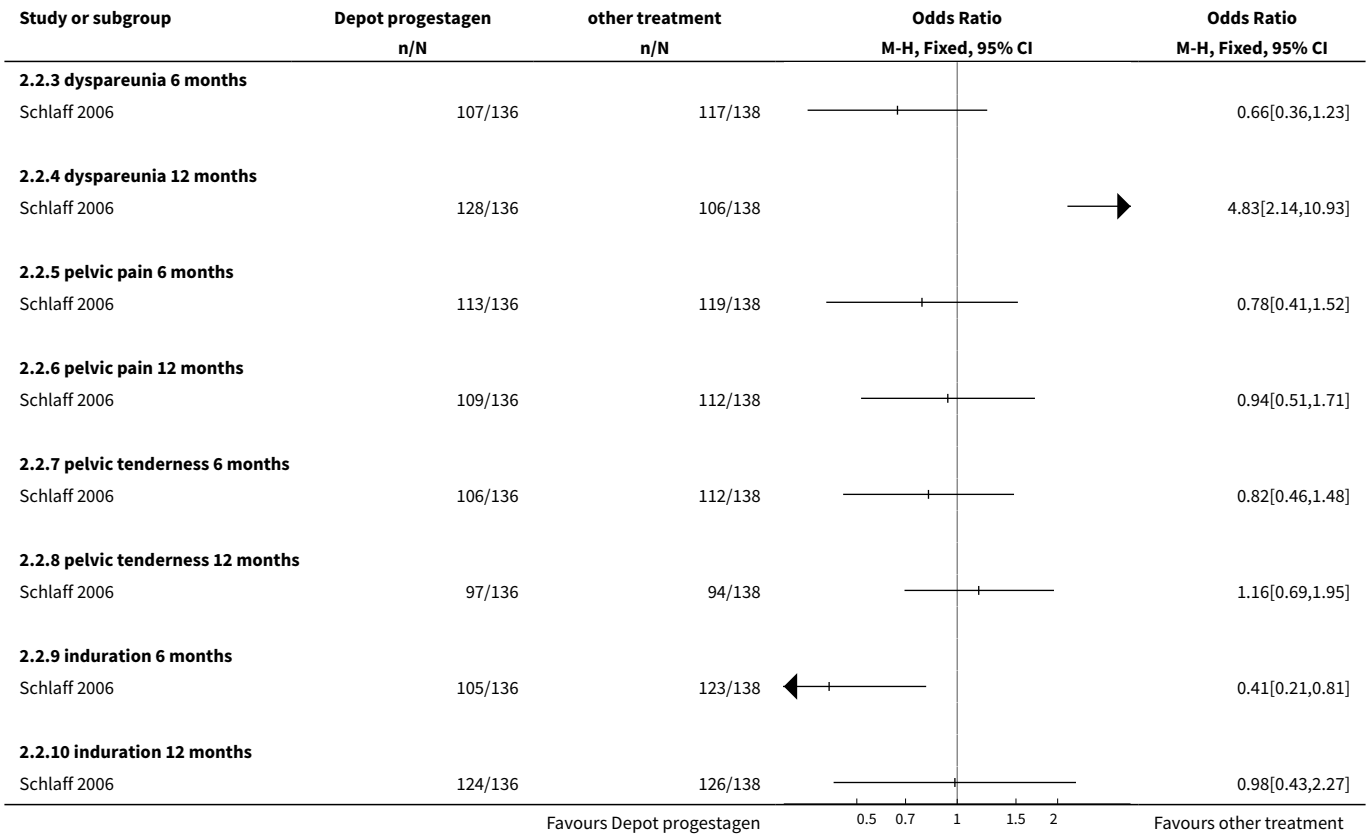
Analysis 2.1. Comparison 2 Depot progestagen versus other treatment, Outcome 1 Patient assessed efficacy during and at end of treatment (6 and 12 months).

Patient assessed efficacy during and at end of treatment (6 and 12 months)					
Study	**Heading 1**	**Heading 2**	**Heading 3**	**Heading 4**	**Heading 5**
painful periods, visual analogue scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 7 (5-10) and 6.5 (5.1-8.2) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-3) and 2 (0.5-3.3) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 0.5 (0-1.5) respectively		
painful periods, verbal rating scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 2 (1-3) and 2 (1-3) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 1 (0-1) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 0 (0-0) respectively		
pain on intercourse, visual analogue scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 4 (0-8) and 3.5 (0-8.1) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-2.7) and 0 (0-3.2) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 0 (0-0.5) respectively		
pain on intercourse, verbal rating scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 1 (0-2) and 1 (0-2) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-1) and 0 (0-1) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 0 (0-0) respectively		
non-menstrual pain, visual analogue scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 4 (0-7.5) and 4.1 (1-7.3) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0.2 (0-3) and 0 (0-2) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-1) and 0 (0-0.5) respectively		
non-menstrual pain, verbal rating scale					
Vercellini 1996	Baseline values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 1 (0-2) and 1 (0-2) respectively	Month six values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-1) and 0 (0-0.1) respectively	Month twelve values (range) for depot medroxyprogesterone acetate and oral contraceptive plus danazol were 0 (0-0) and 0 (0-0) respectively		

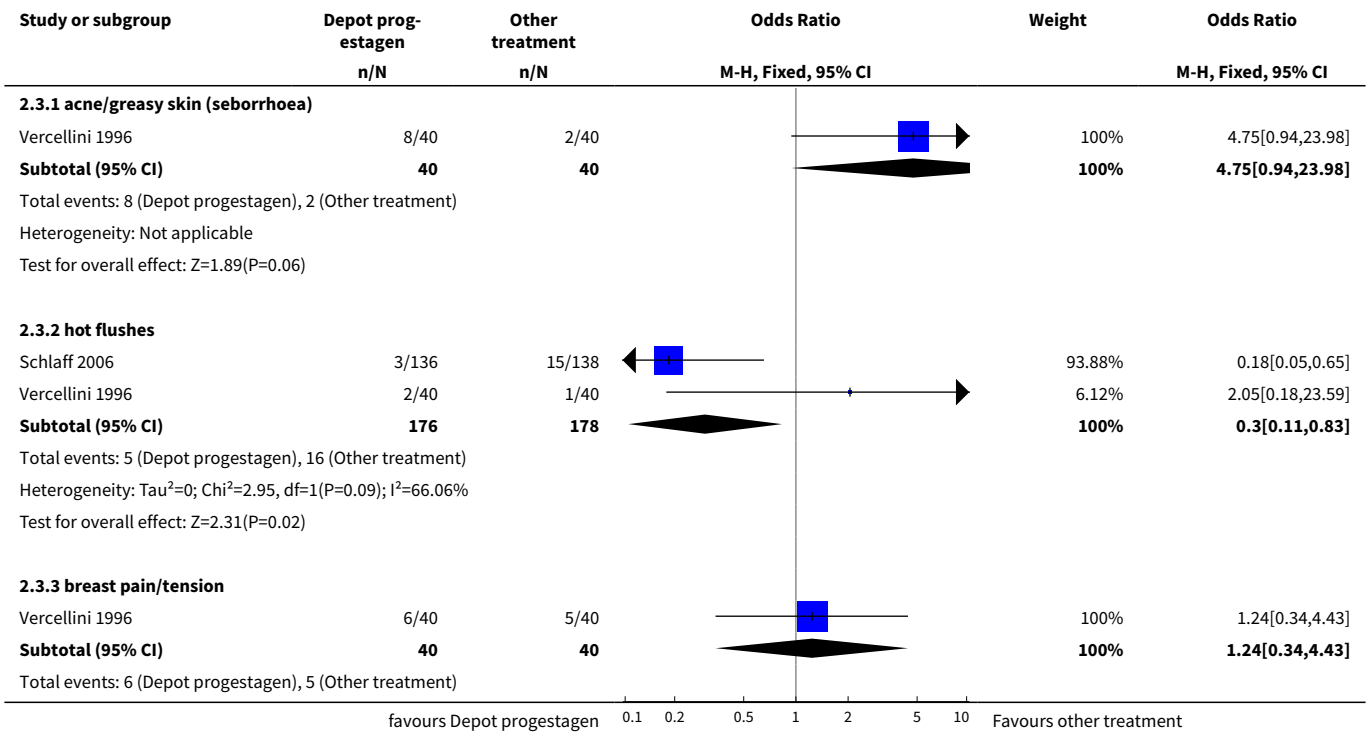
Analysis 2.2. Comparison 2 Depot progestagen versus other treatment, Outcome 2 Improvement in symptoms.

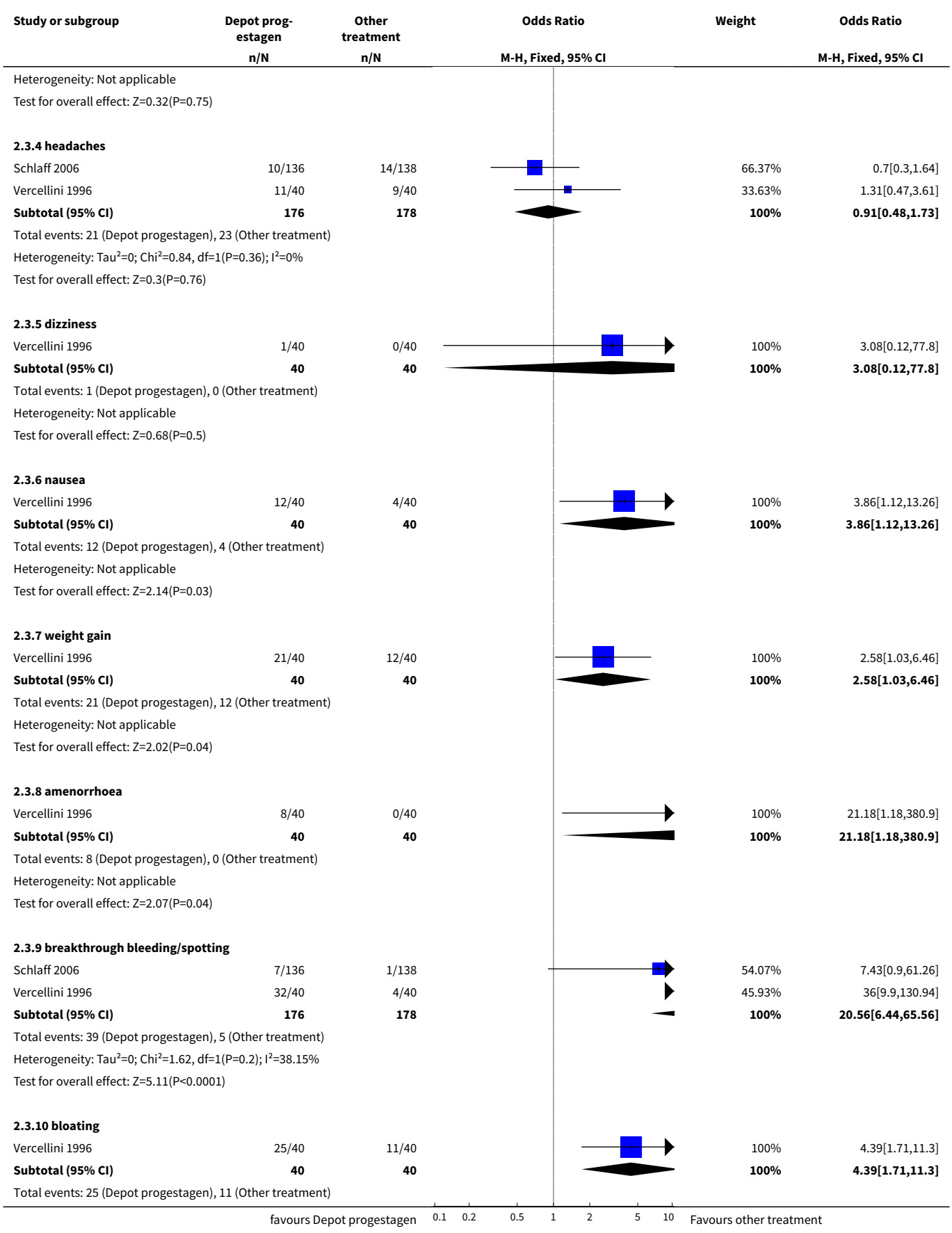
Study or subgroup	Depot progestagen n/N	other treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.2.1 dysmenorrhoea 6 months				
Schlaff 2006	122/136	135/138		0.19[0.05,0.69]
2.2.2 dysmenorrhoea 12 months				
Schlaff 2006	92/136	106/138		0.63[0.37,1.08]

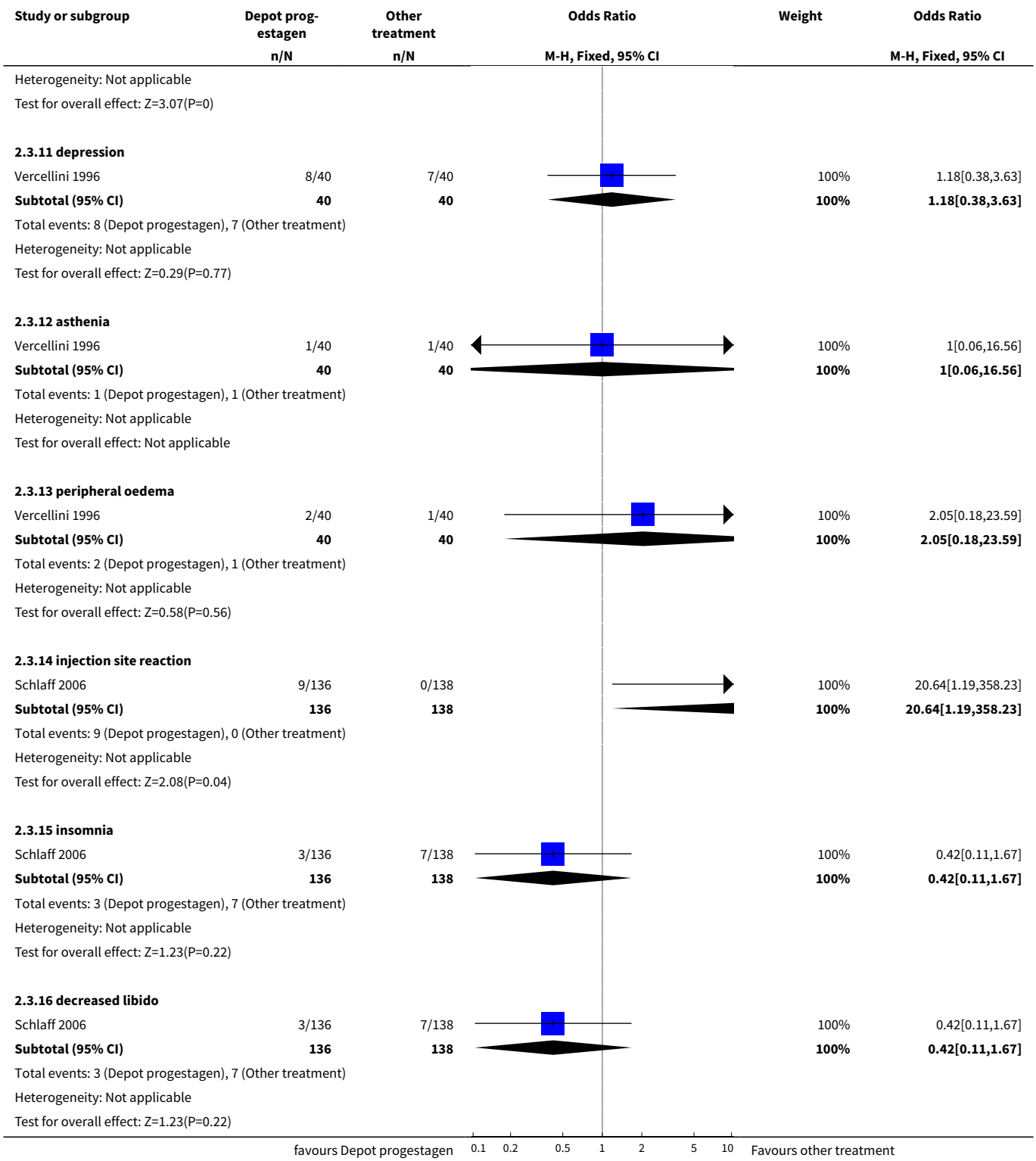




Analysis 2.3. Comparison 2 Depot progestagen versus other treatment, Outcome 3 Side effects.







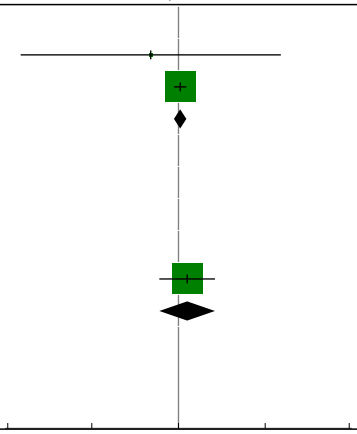
Comparison 3. Oral progestagens versus other treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient assessed efficacy (6 months)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 pain	2	286	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.26, 0.46]
1.2 sum of all symptoms	1	34	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.10, 2.10]
2 Patient assessed efficacy, 4 point verbal rating scale at end of follow-up (12 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 pelvic pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 sum of all symptoms	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Objective efficacy at end of follow-up (12 months)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 AFS score	2	302	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.01, 0.70]
4 Improved VAS score	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Quality of life	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 physical health summary scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 mental health summary scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 bodily pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Severe/very severe signs and symptoms (24 weeks)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Change in pain from baseline to 24 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 abdominal pain	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 lumbago	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Pain symptom scores			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Self reported pain			Other data	No numeric data
10 Side effects			Other data	No numeric data
11 Side effects	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 acne	2	286	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.24, 1.49]
11.2 oedema	1	34	Odds Ratio (M-H, Fixed, 95% CI)	2.75 [0.67, 11.24]
11.3 muscle cramps	1	34	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.09, 2.27]
11.4 spotting	2	124	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.54]
11.5 headache	3	613	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.87]
11.6 weight gain	2	342	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.51, 2.33]
11.7 depression	2	342	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.37, 1.97]
11.8 decreased libido	2	342	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.52, 2.94]
11.9 hair loss	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.16, 2.02]
11.10 migraine	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.12, 2.06]
11.11 sleep disorder	1	252	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.90]
11.12 vaginal dryness	2	342	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.15, 1.48]
11.13 hot flushes	3	613	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.31, 0.76]
11.14 study withdrawal due to side effects	1	252	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.37, 4.21]
11.15 genital bleeding	1	271	Odds Ratio (M-H, Fixed, 95% CI)	4.69 [2.47, 8.90]
11.16 amenorrhoea	1	252	Odds Ratio (M-H, Fixed, 95% CI)	4.95 [2.88, 8.52]
11.17 bloating or swelling	1	90	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.37, 2.19]
11.18 irritability	1	90	Odds Ratio (M-H, Fixed, 95% CI)	3.14 [0.31, 31.42]
11.19 nausea	1	90	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.94]

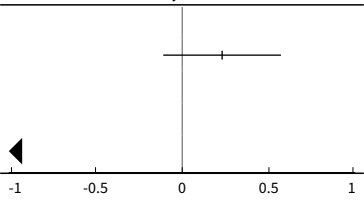
Analysis 3.1. Comparison 3 Oral progestagens versus other treatment, Outcome 1 Patient assessed efficacy (6 months).

Study or subgroup	Progestagen N	Progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 pain							
Strowitzki 2010	124	40.2 (32)	128	41.8 (28.6)		0.23%	-1.6[-9.1,5.9]
Telimaa 1987b	16	0.5 (0.5)	18	0.4 (0.6)		99.77%	0.1[-0.26,0.46]
Subtotal ***	**140**		**146**			**100%**	**0.1[-0.26,0.46]**
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.66); I²=0%							
Test for overall effect: Z=0.52(P=0.6)							
3.1.2 sum of all symptoms							
Telimaa 1987b	16	1.4 (1.8)	18	0.9 (2.9)		100%	0.5[-1.1,2.1]
Subtotal ***	**16**		**18**			**100%**	**0.5[-1.1,2.1]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=0.61(P=0.54)							
Test for subgroup differences: Chi²=0.23, df=1 (P=0.63), I²=0%							



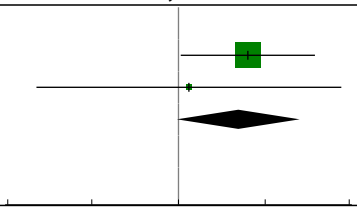
Analysis 3.2. Comparison 3 Oral progestagens versus other treatment, Outcome 2 Patient assessed efficacy, 4 point verbal rating scale at end of follow-up (12 months).

Study or subgroup	Oral progestagen N	Oral progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.2.1 pelvic pain						
Telimaa 1987b	15	1 (0.5)	17	0.7 (0.5)		0.23[-0.11,0.57]
3.2.2 sum of all symptoms						
Telimaa 1987b	15	3.4 (1.7)	17	6.8 (2.4)		-3.4[-4.83,-1.97]



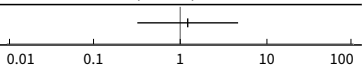
Analysis 3.3. Comparison 3 Oral progestagens versus other treatment, Outcome 3 Objective efficacy at end of follow-up (12 months).

Study or subgroup	oral progestagen N	oral progestagen Mean(SD)	other treatment N	other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.3.1 AFS score							
Harada 2009	137	1.9 (1.9)	134	1.5 (1.3)		83.77%	0.4[0.01,0.79]
Telimaa 1987b	16	1.2 (1.4)	15	1.1 (1.1)		16.23%	0.06[-0.82,0.94]
Subtotal ***	**153**		**149**			**100%**	**0.34[-0.01,0.7]**
Heterogeneity: Tau²=0; Chi²=0.48, df=1(P=0.49); I²=0%							
Test for overall effect: Z=1.91(P=0.06)							



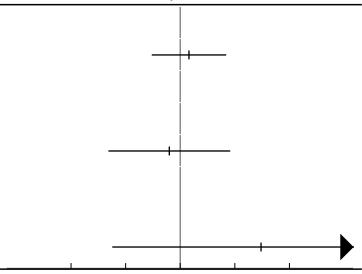
Analysis 3.4. Comparison 3 Oral progestagens versus other treatment, Outcome 4 Improved VAS score.

Study or subgroup	oral progestagen n/N	other treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Strowitzki 2010	120/124	123/128		1.22[0.32,4.65]



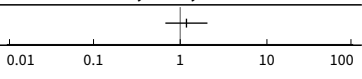
Analysis 3.5. Comparison 3 Oral progestagens versus other treatment, Outcome 5 Quality of life.

Study or subgroup	Oral progestagen N	Oral progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.5.1 physical health summary scale						
Strowitzki 2010	124	51.6 (6.7)	128	51.2 (7.1)		0.4[-1.3,2.1]
3.5.2 mental health summary scale						
Strowitzki 2010	124	45.4 (10.9)	128	45.9 (11.7)		-0.5[-3.29,2.29]
3.5.3 bodily pain						
Harada 2009	137	22.2 (28.4)	134	18.5 (28.8)		3.7[-3.11,10.51]



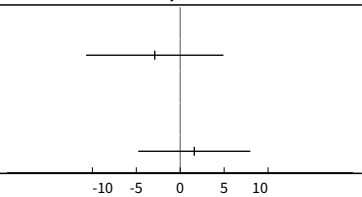
Analysis 3.6. Comparison 3 Oral progestagens versus other treatment, Outcome 6 Severe/very severe signs and symptoms (24 weeks).

Study or subgroup	Oral progestagen n/N	other treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Strowitzki 2010	35/124	32/128		1.18[0.67,2.06]



Analysis 3.7. Comparison 3 Oral progestagens versus other treatment, Outcome 7 Change in pain from baseline to 24 weeks.

Study or subgroup	oral progestagen N	oral progestagen Mean(SD)	other treatment N	other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.7.1 abdominal pain						
Harada 2009	137	-30.2 (31.8)	134	-27.3 (33.8)		-2.9[-10.72,4.92]
3.7.2 lumbago						
Harada 2009	137	-15.7 (28.7)	134	-17.3 (24.8)		1.6[-4.78,7.98]



Analysis 3.8. Comparison 3 Oral progestagens versus other treatment, Outcome 8 Pain symptom scores.

Study	6 months	Pain symptom scores: Cyproterone acetate Visual analogue scale	Cyproterone acetate Verbal rating scale	Oral contraceptiveVisual analogue scale	Oral contraceptiveVerbal scale
Vercellini 2002	Dysmenorrhoea	0 (0 - 0)	2 (1 - 2)	74 (59 - 83)	

Study	6 months	Pain symptom scores Cyproterone acetate Visual analogue scale	Cyproterone acetate Verbal rating scale	Oral contraceptiveVisual analogue scale	Oral contraceptiveVerbal scale
	Median (IQR)	n=39	n=39	n=36	
Vercellini 2002	Deep dyspareunia Median (IQR)	13 (10 - 30) n= 23	0 (0 - 1) n=23	15 (0 - 20) n = 25	0 (0 - 1) n = 25
Vercellini 2002	Non Menstrual pain Median (IQR)	14 (0 - 40) n = 22	0 (0 - 1) n = 22	20 (0 - 30) n = 20	0 (0 - 1) n = 20

Analysis 3.9. Comparison 3 Oral progestagens versus other treatment, Outcome 9 Self reported pain.

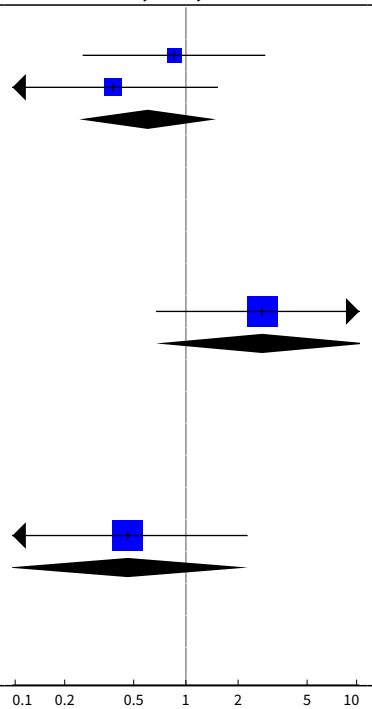
Study	Self reported pain
Razzi 2007	Both desogestrel and the oral contraceptive showed significant decreases in self reported pain compared to baseline P <0.001. After 6 months the mean VAS score for desogestrel alone was 2.5 and for the oral contraceptive was 2.3. There was no statistical comparison between groups calculated.

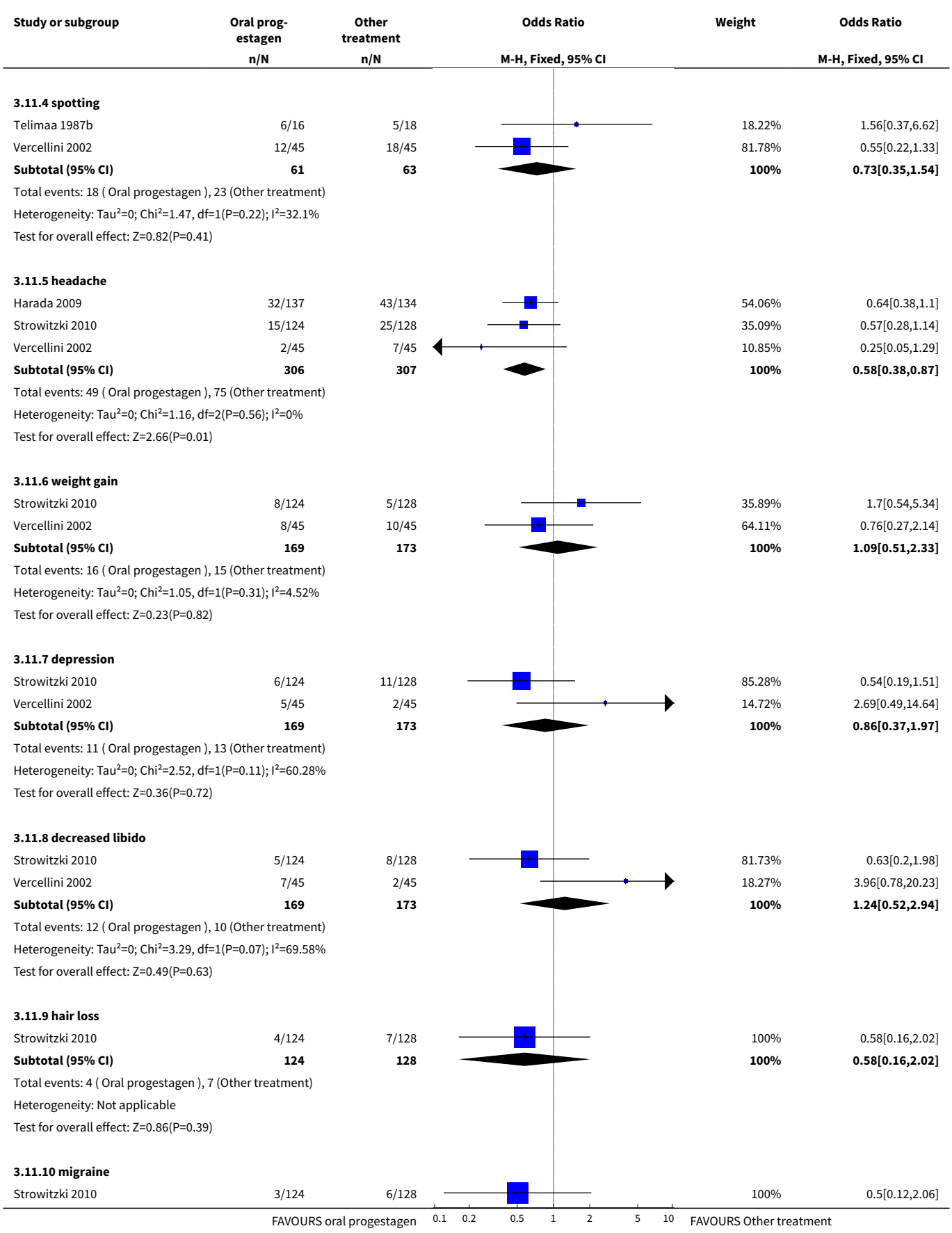
Analysis 3.10. Comparison 3 Oral progestagens versus other treatment, Outcome 10 Side effects.

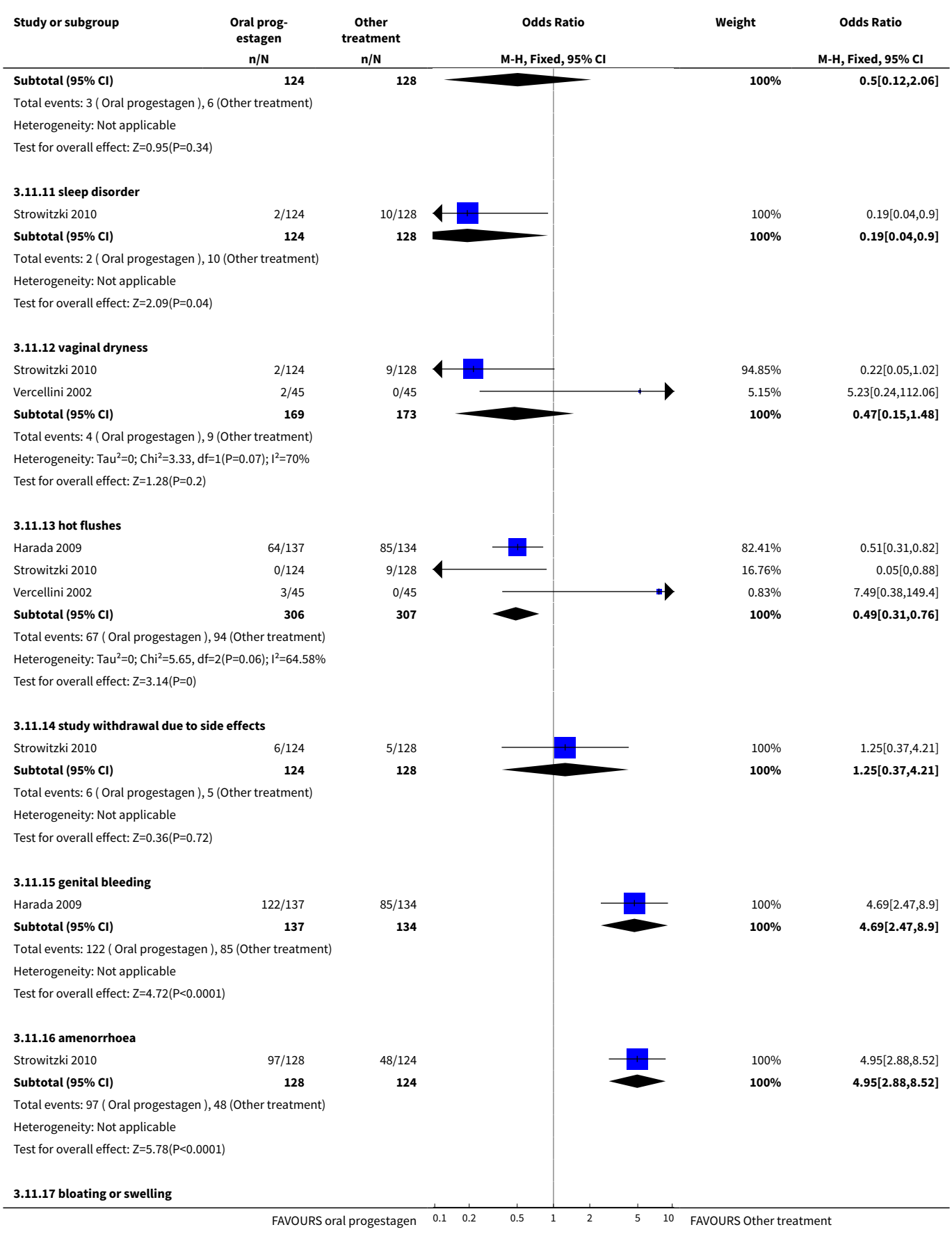
Study	Side effects
Razzi 2007	The authors report on breakthrough bleeding in 4/20 patients randomised to desogestrel and increased body weight in 3/20 randomised to oral contraceptive. no other details provided

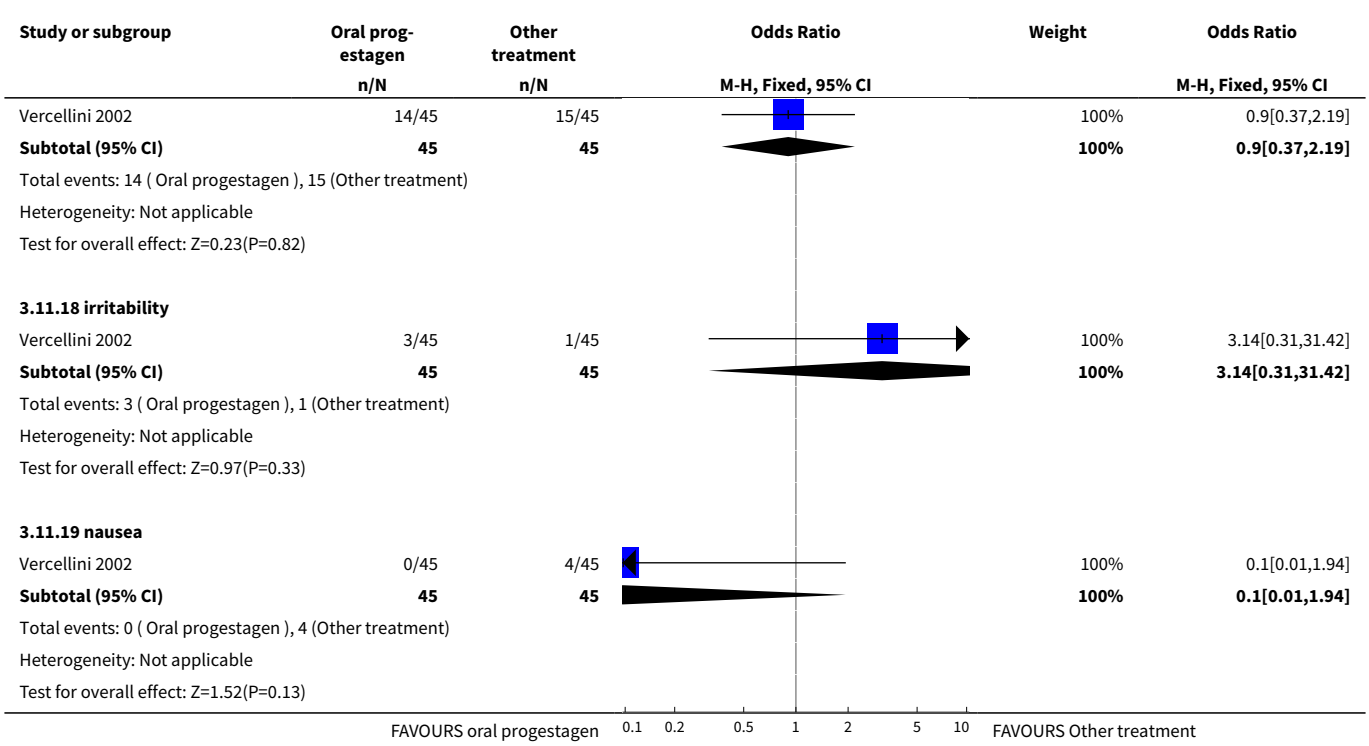
Analysis 3.11. Comparison 3 Oral progestagens versus other treatment, Outcome 11 Side effects.

Study or subgroup	Oral progestagen n/N	Other treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.11.1 acne					
Strowitzki 2010	5/124	6/128		46.69%	0.85[0.25,2.87]
Telimaa 1987b	6/16	11/18		53.31%	0.38[0.1,1.53]
Subtotal (95% CI)	**140**	**146**		**100%**	**0.6[0.24,1.49]**
Total events: 11 (Oral progestagen), 17 (Other treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=1.1(P=0.27)					
3.11.2 oedema					
Telimaa 1987b	11/16	8/18		100%	2.75[0.67,11.24]
Subtotal (95% CI)	**16**	**18**		**100%**	**2.75[0.67,11.24]**
Total events: 11 (Oral progestagen), 8 (Other treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
3.11.3 muscle cramps					
Telimaa 1987b	3/16	6/18		100%	0.46[0.09,2.27]
Subtotal (95% CI)	**16**	**18**		**100%**	**0.46[0.09,2.27]**
Total events: 3 (Oral progestagen), 6 (Other treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					









Comparison 4. Anti-progestagen versus other treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Patient assessed efficacy at end of treatment (6 months)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 none or mild pelvic pain	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.56]
1.2 none or mild painful periods (dysmenorrhoea)	2	214	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.39, 1.33]
1.3 none or mild pain on intercourse (dyspareunia)	2	222	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.37, 1.86]
2 Patient assessed efficacy 6 months after the end of treatment	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 none or mild pelvic pain	2	202	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.58, 2.48]
2.2 none or mild painful periods (dysmenorrhoea)	2	176	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.55, 1.93]
2.3 none or mild pain on intercourse (dyspareunia)	2	192	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.42, 2.09]

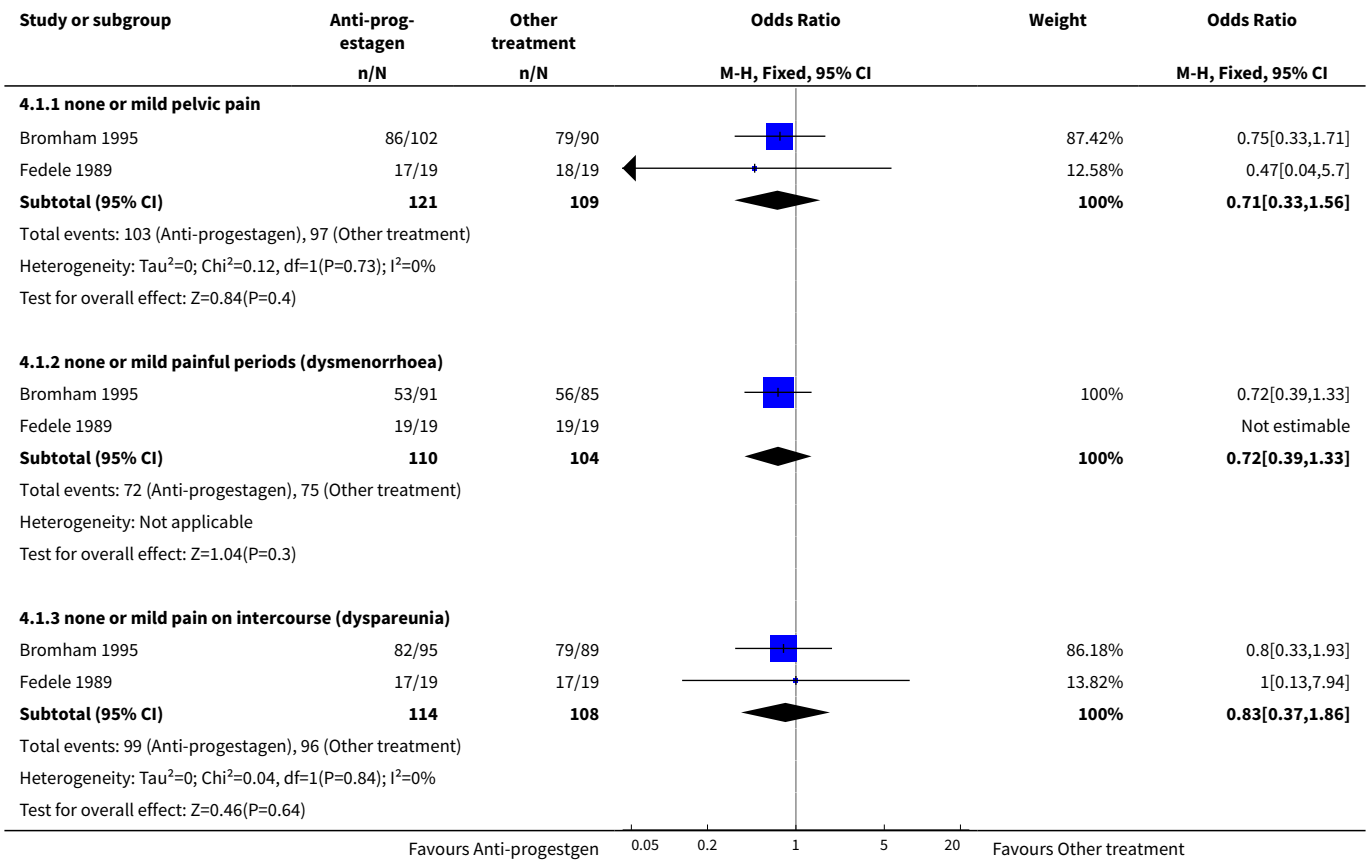
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Objective assessment of efficacy at end of treatment (6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 rAFS scores	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 implant score	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Patient assessed efficacy at end of treatment (6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 painful periods, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 painful periods, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 pain on intercourse, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 pain on intercourse, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.5 non-menstrual pain, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 non-menstrual pain, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Patient assessed efficacy at end of follow-up (12 months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 painful periods, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 painful periods, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 pain on intercourse, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 pain on intercourse, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.5 non-menstrual pain, visual analogue scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 non-menstrual pain, verbal rating scale	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Side effects	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 acne	2	302	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.90, 2.33]
6.2 seborrhoea	3	357	Odds Ratio (M-H, Fixed, 95% CI)	2.74 [1.69, 4.46]
6.3 hirsutism	2	302	Odds Ratio (M-H, Fixed, 95% CI)	2.63 [1.60, 4.32]
6.4 voice problems	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.43]
6.5 swelling hands/feet	2	319	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.88, 2.48]
6.6 hot flushes	3	357	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 0.99]
6.7 sweating problems	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.88, 2.35]
6.8 loss of libido	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.80, 2.19]
6.9 decreased breast size	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 0.98]
6.10 leg or muscle cramps	3	357	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.30, 0.77]
6.11 headaches	2	319	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.64, 1.53]
6.12 nausea	3	357	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.84, 2.16]
6.13 vomiting	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.32, 1.43]
6.14 loss of appetite	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.72, 2.37]
6.15 hunger	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.97]
6.16 dizziness	2	319	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.77, 2.08]
6.17 tiredness	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.84, 2.45]
6.18 faintness	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.54, 2.76]

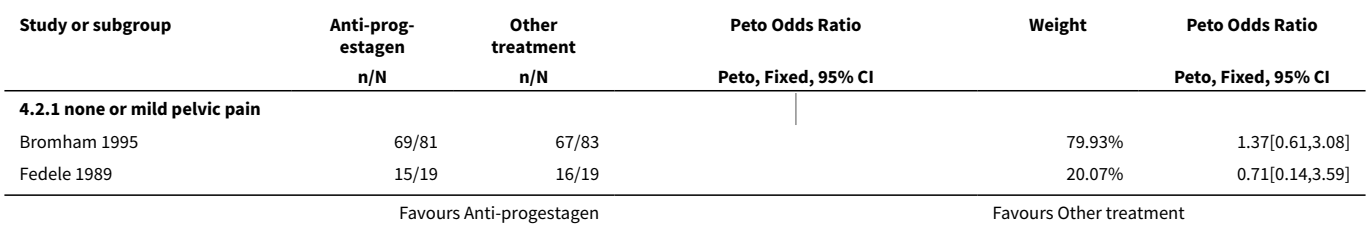
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.19 skin rash	2	319	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [0.95, 3.24]
6.20 weight gain	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.27]
6.21 vaginal dryness	2	93	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.66]
6.22 raised liver transaminases	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.00]
6.23 stopped treatment because of side effects	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.47, 1.57]
6.24 asthenia	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.8 [0.19, 3.36]
6.25 mood changes	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.10, 4.34]
6.26 dermatitis	1	55	Odds Ratio (M-H, Fixed, 95% CI)	8.14 [0.40, 165.53]
6.27 joint pain	1	55	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.18, 25.32]
6.28 drowsiness	1	55	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.18, 25.32]
6.29 tachycardia	1	55	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.49]
6.30 insomnia	1	55	Odds Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 82.71]
6.31 hypertrichosis	1	55	Odds Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 82.71]
6.32 constipation	1	55	Odds Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 82.71]
6.33 itching	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.55]
6.34 vaginal discharge	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.55]
6.35 parasthesia	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.55]
6.36 suffered any side effect	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.20, 1.77]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.37 amenorrhoea	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.38]
6.38 spotting or bleeding	1	49	Odds Ratio (M-H, Fixed, 95% CI)	22.92 [2.64, 198.66]

Analysis 4.1. Comparison 4 Anti-progestagen versus other treatment, Outcome 1 Patient assessed efficacy at end of treatment (6 months).



Analysis 4.2. Comparison 4 Anti-progestagen versus other treatment, Outcome 2 Patient assessed efficacy 6 months after the end of treatment.



Study or subgroup	Anti-progestagen n/N	Other treatment n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Subtotal (95% CI)	**100**	**102**		**100%**	**1.2[0.58,2.48]**
Total events: 84 (Anti-progestagen), 83 (Other treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%					
Test for overall effect: Z=0.49(P=0.62)					
4.2.2 none or mild painful periods (dysmenorrhoea)					
Bromham 1995	44/67	44/71		83.19%	1.17[0.59,2.34]
Fedele 1989	14/19	16/19		16.81%	0.54[0.12,2.52]
Subtotal (95% CI)	**86**	**90**		**100%**	**1.03[0.55,1.93]**
Total events: 58 (Anti-progestagen), 60 (Other treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
4.2.3 none or mild pain on intercourse (dyspareunia)					
Bromham 1995	64/74	70/80		72.95%	0.91[0.36,2.34]
Fedele 1989	15/19	15/19		27.05%	1[0.21,4.66]
Subtotal (95% CI)	**93**	**99**		**100%**	**0.94[0.42,2.09]**
Total events: 79 (Anti-progestagen), 85 (Other treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.9), I^2=0%					

Favours Anti-progestagen | Favours Other treatment

Analysis 4.3. Comparison 4 Anti-progestagen versus other treatment, Outcome 3 Objective assessment of efficacy at end of treatment (6 months).

Study or subgroup	Antiprogestagen N	Antiprogestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.3.1 rAFS scores						
Fedele 1989	7	13.2 (8.6)	9	11.8 (7.8)		1.4[-6.76,9.56]
4.3.2 implant score						
Fedele 1989	7	8.2 (8.8)	9	7.1 (5.3)		1.1[-6.28,8.48]

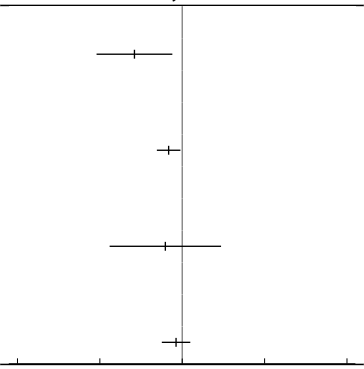
Favours Anti-progestagen -10 -5 0 5 10 Favours Other treatment

Analysis 4.4. Comparison 4 Anti-progestagen versus other treatment, Outcome 4 Patient assessed efficacy at end of treatment (6 months).

Study or subgroup	Anti-progestagen N	Anti-progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.4.1 painful periods, visual analogue scale						
GISG 1996	27	0.9 (1.8)	28	0.1 (0.2)		0.82[0.15,1.49]
4.4.2 painful periods, verbal rating scale						
GISG 1996	27	0.4 (0.6)	28	0 (0.2)		0.35[0.12,0.58]

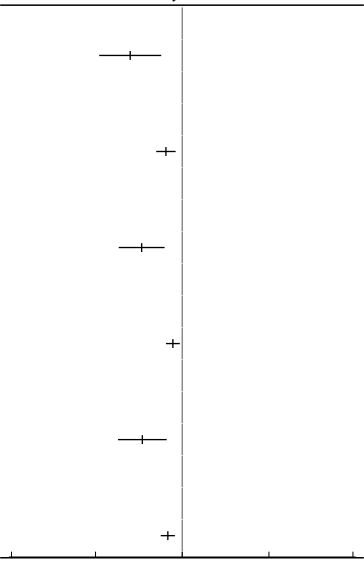
Favours Other treatment -4 -2 0 2 4 Favours Anti-progestagen

Study or subgroup	Anti-progestagen N	Anti-progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.4.3 pain on intercourse, visual analogue scale						
GISG 1996	26	0.4 (1.1)	26	1.6 (2.1)		-1.16[-2.08,-0.24]
4.4.4 pain on intercourse, verbal rating scale						
GISG 1996	26	0.1 (0.3)	26	0.4 (0.7)		-0.33[-0.62,-0.04]
4.4.5 non-menstrual pain, visual analogue scale						
GISG 1996	27	1.2 (2.7)	28	1.6 (2.5)		-0.41[-1.76,0.94]
4.4.6 non-menstrual pain, verbal rating scale						
GISG 1996	27	0.4 (0.7)	28	0.5 (0.6)		-0.15[-0.5,0.2]



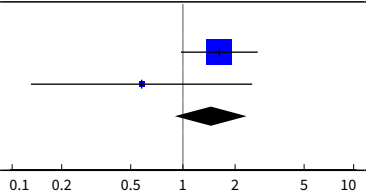
Analysis 4.5. Comparison 4 Anti-progestagen versus other treatment, Outcome 5 Patient assessed efficacy at end of follow-up (12 months).

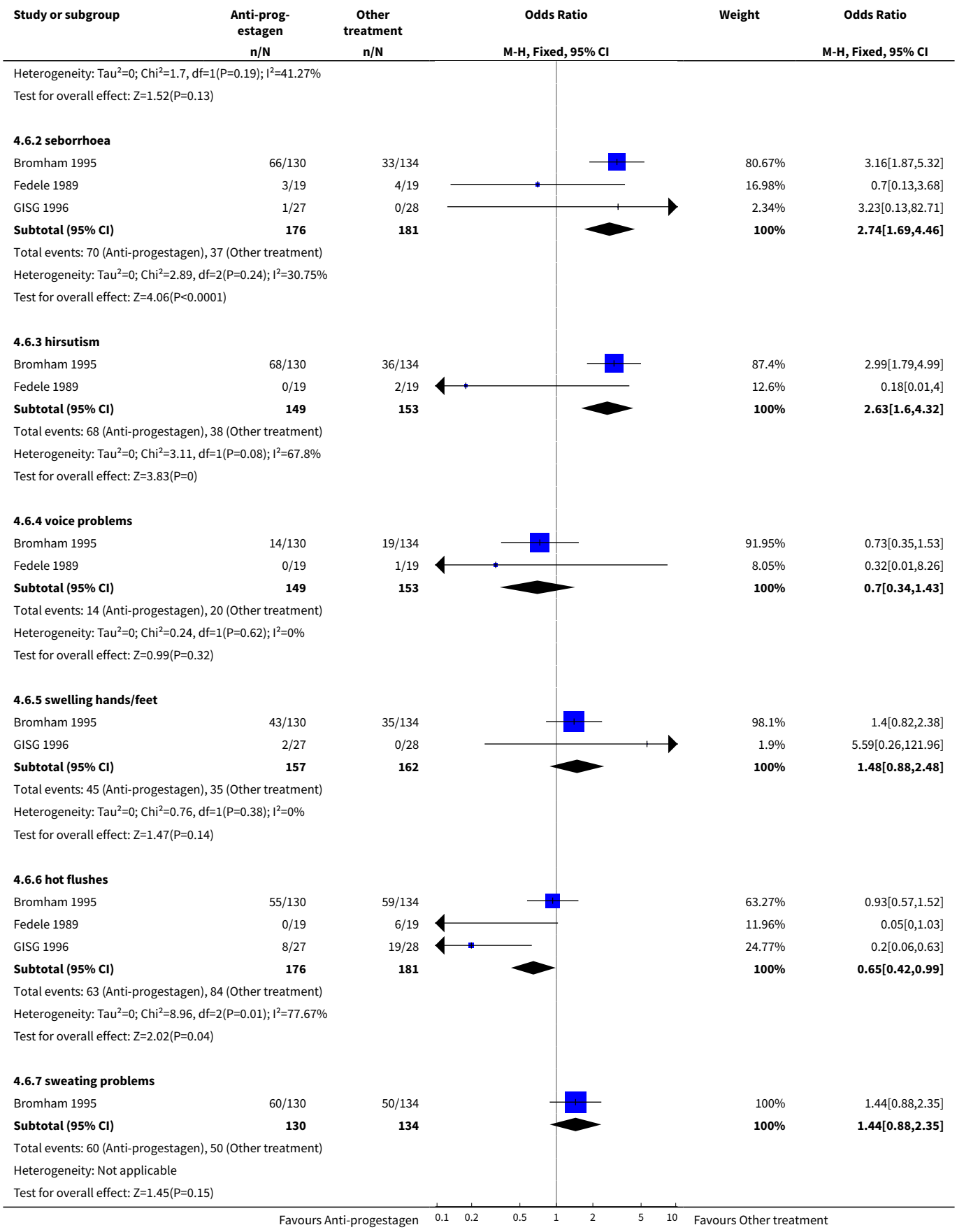
Study or subgroup	Anti-progestagen N	Anti-progestagen Mean(SD)	Other treatment N	Other treatment Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.5.1 painful periods, visual analogue scale						
GISG 1996	27	1.8 (3.1)	28	4.8 (3.6)		-3[-4.79,-1.21]
4.5.2 painful periods, verbal rating scale						
GISG 1996	27	0.7 (0.9)	28	1.6 (1.2)		-0.94[-1.5,-0.38]
4.5.3 pain on intercourse, visual analogue scale						
GISG 1996	26	0.3 (0.4)	26	2.6 (3.4)		-2.34[-3.66,-1.02]
4.5.4 pain on intercourse, verbal rating scale						
GISG 1996	26	0.1 (0.3)	26	0.7 (1)		-0.54[-0.94,-0.14]
4.5.5 non-menstrual pain, visual analogue scale						
GISG 1996	27	1.1 (1.5)	28	3.4 (3.5)		-2.3[-3.7,-0.9]
4.5.6 non-menstrual pain, verbal rating scale						
GISG 1996	27	0.3 (0.5)	28	1.1 (1)		-0.83[-1.24,-0.42]

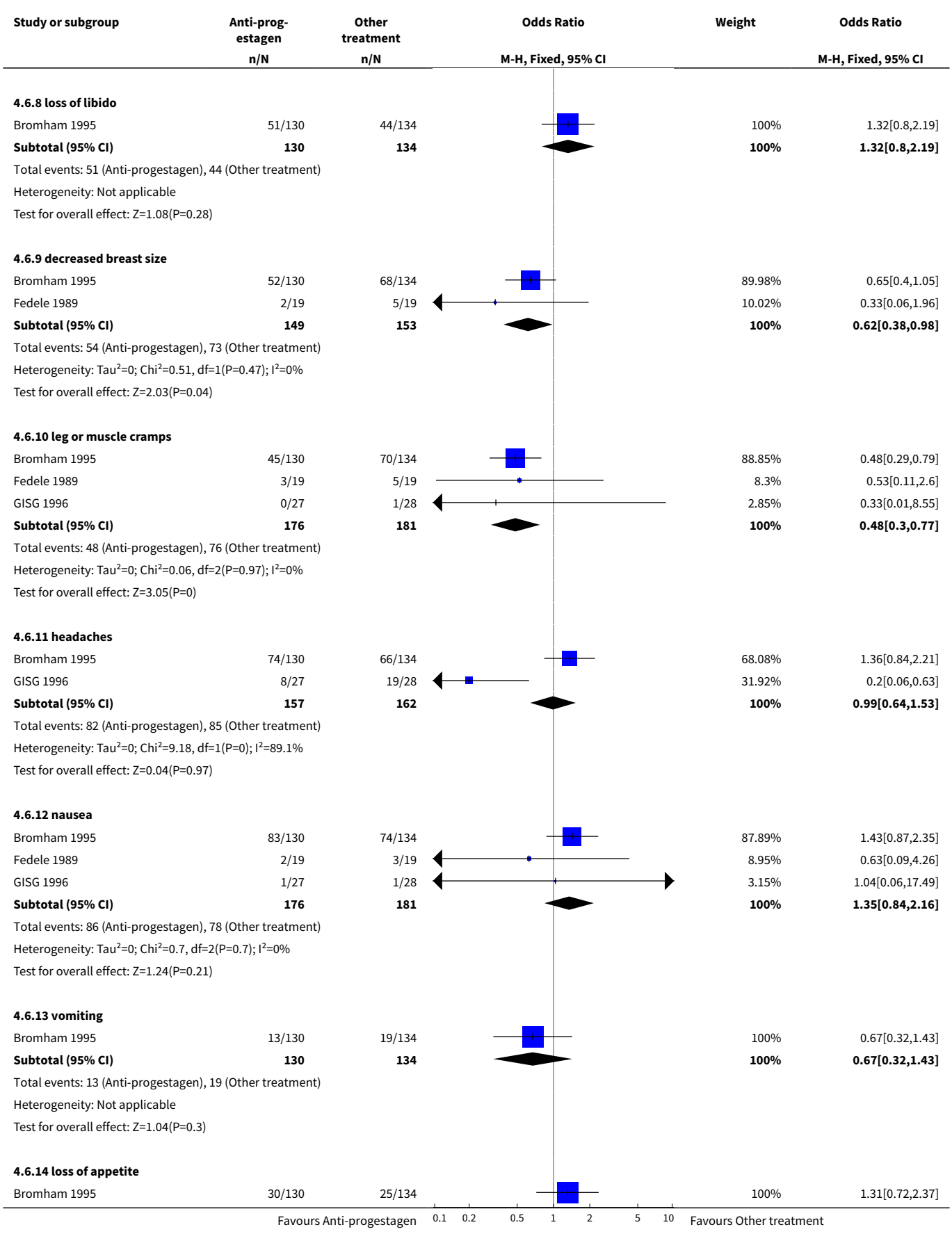


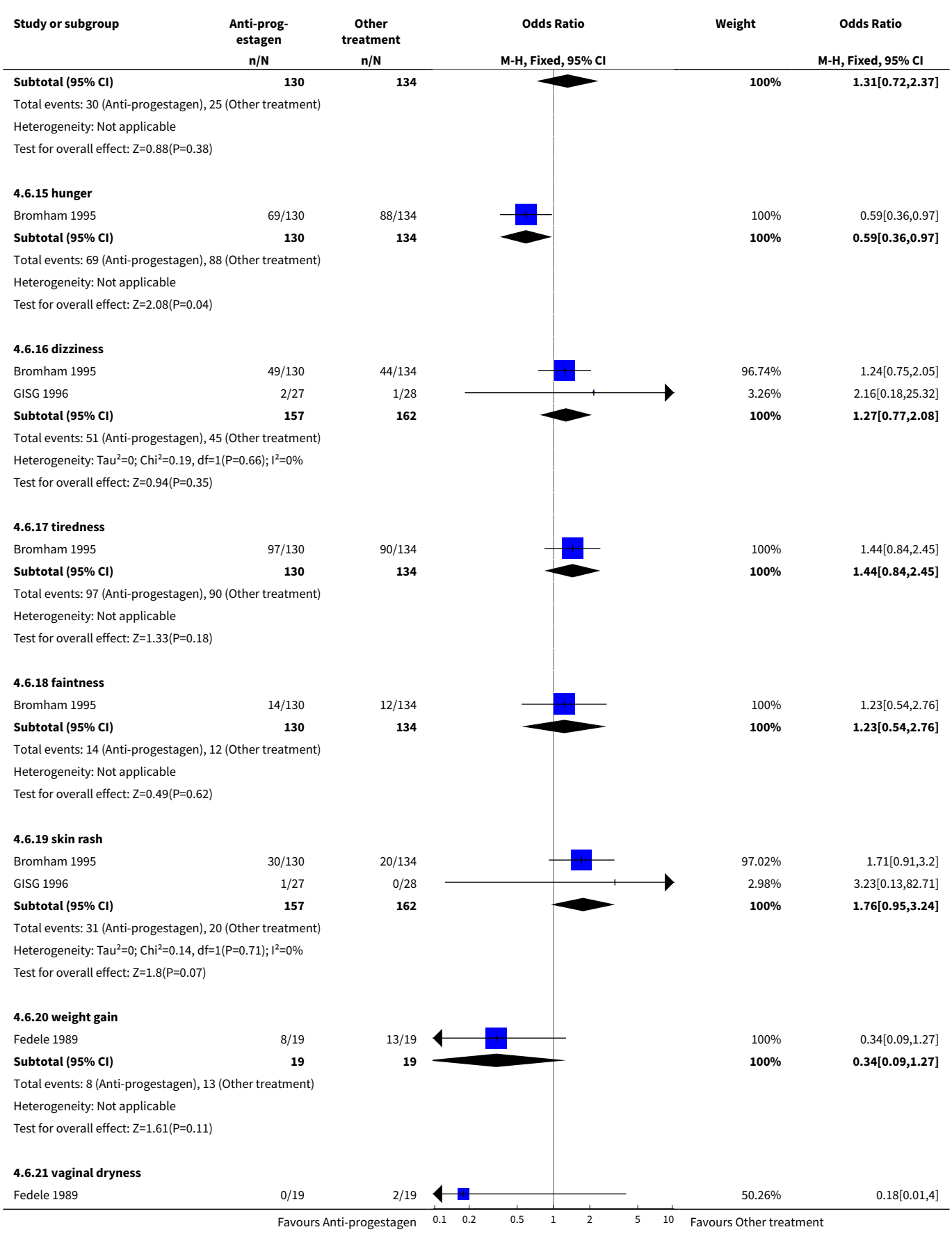
Analysis 4.6. Comparison 4 Anti-progestagen versus other treatment, Outcome 6 Side effects.

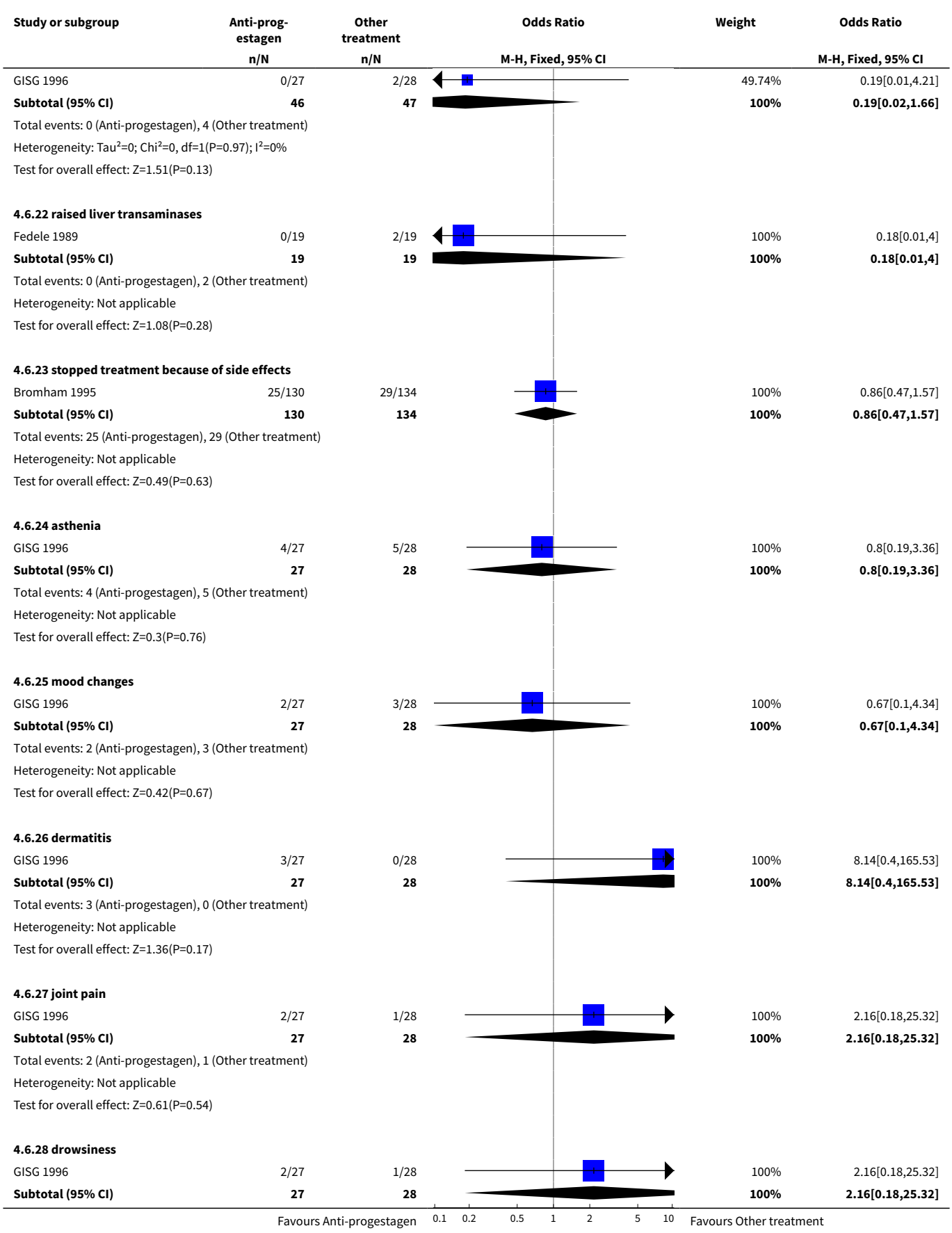
Study or subgroup	Anti-progestagen n/N	Other treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.6.1 acne					
Bromham 1995	91/130	79/134		83.13%	1.62[0.98,2.7]
Fedele 1989	4/19	6/19		16.87%	0.58[0.13,2.51]
Subtotal (95% CI)	**149**	**153**		**100%**	**1.45[0.9,2.33]**
Total events: 95 (Anti-progestagen), 85 (Other treatment)					

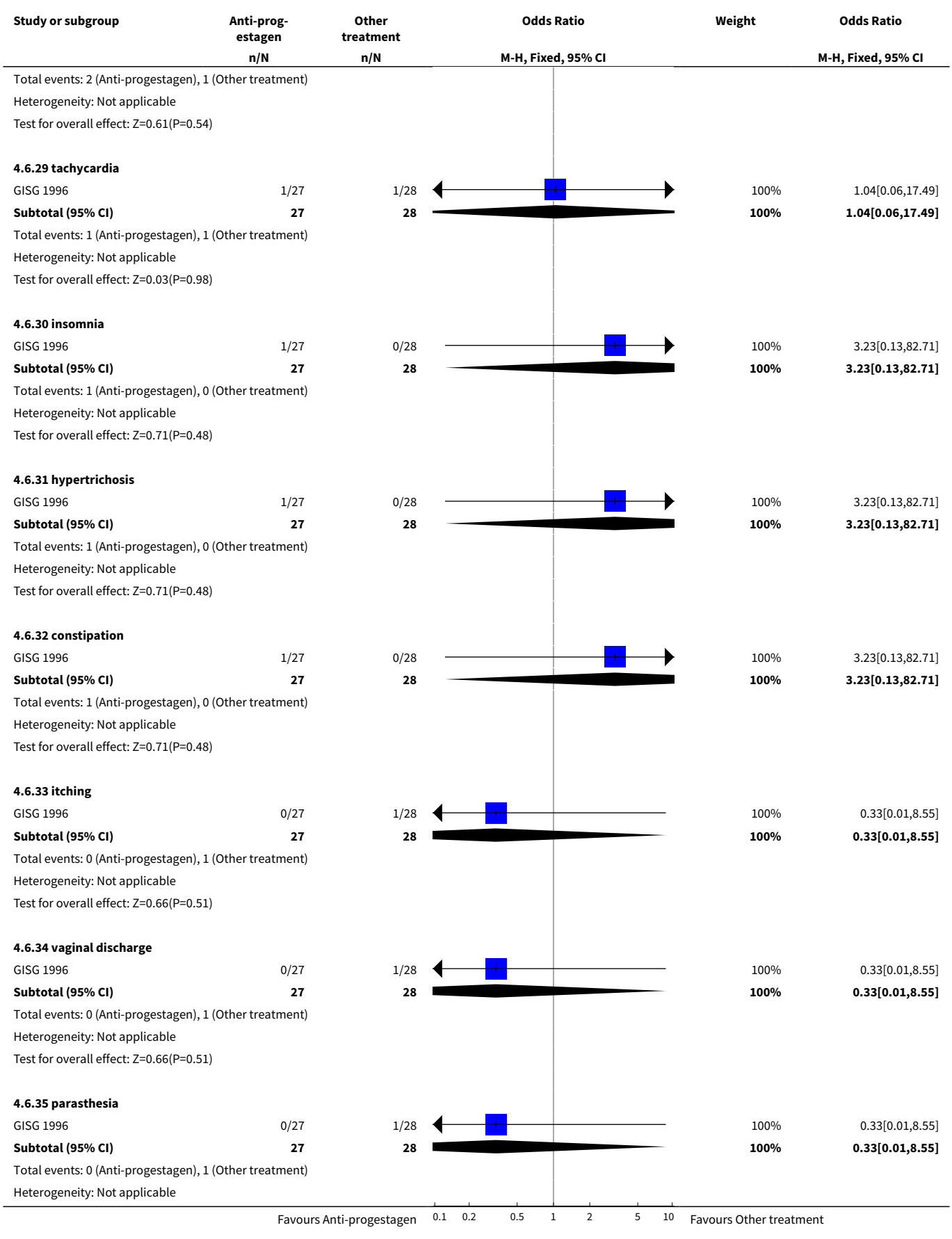


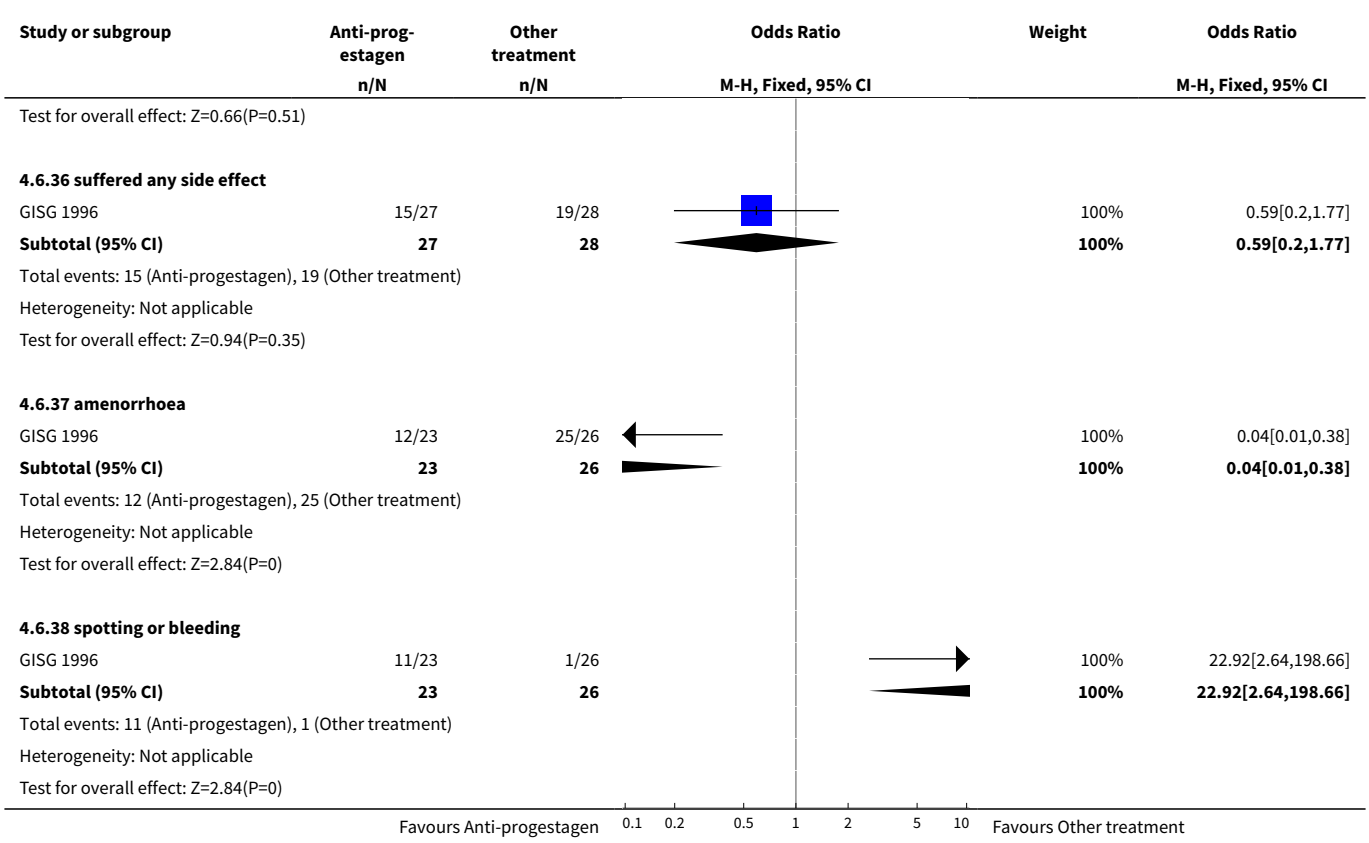










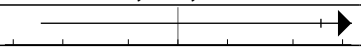


Comparison 5. Antiprogestagens (varying dosage)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Subjective improvement in pain	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 Objective efficacy - rAFS scores at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Side effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 noted any side effect	1	12	Odds Ratio (M-H, Fixed, 95% CI)	23.40 [0.89, 612.98]
3.2 discontinued treatment because of headaches	1	12	Odds Ratio (M-H, Fixed, 95% CI)	3.55 [0.12, 105.82]
3.3 discontinued treatment because of continuing pain	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 8.42]
3.4 suffered from irregular bleeding	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.4 [0.03, 6.18]

Analysis 5.1. Comparison 5 Antiprogestagens (varying dosage), Outcome 1 Subjective improvement in pain.

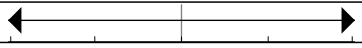
Study or subgroup	Gestrinone 2.5mg n/N	Gestrinone 1.25mg n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hornstein 1990	5/5	4/5		0%	7.39[0.15,372.38]



Favours 2.5mg — Favours 1.25mg

Analysis 5.2. Comparison 5 Antiprogestagens (varying dosage), Outcome 2 Objective efficacy - rAFS scores at 6 months.

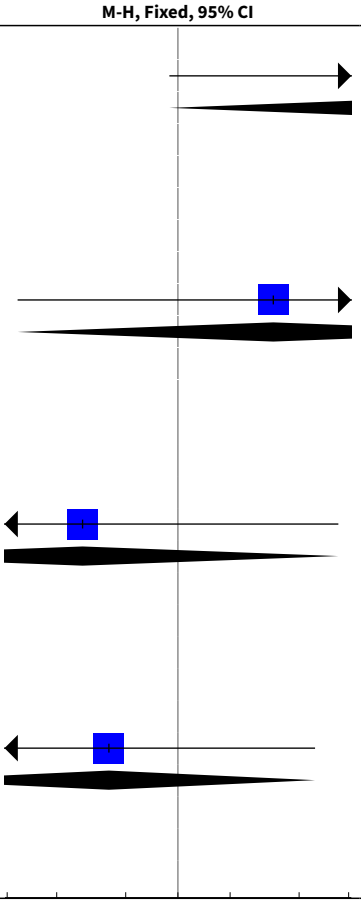
Study or subgroup	Gestrinone 2.5mg N	Gestrinone 2.5mg Mean(SD)	Gestrinone 1.25mg N	Gestrinone 1.25mg Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hornstein 1990	5	7.1 (4.7)	5	9.5 (8.7)		0%	-2.4[-11.07,6.27]



favours 2.5mg — favours 1.25mg

Analysis 5.3. Comparison 5 Antiprogestagens (varying dosage), Outcome 3 Side effects.

Study or subgroup	Gestrinone 2.5mg n/N	Gestrinone 1.25mg n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
5.3.1 noted any side effect					
Hornstein 1990	6/6	2/6		100%	23.4[0.89,612.98]
Subtotal (95% CI)	**6**	**6**		**100%**	**23.4[0.89,612.98]**
Total events: 6 (Gestrinone 2.5mg), 2 (Gestrinone 1.25mg)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.89(P=0.06)					
5.3.2 discontinued treatment because of headaches					
Hornstein 1990	1/6	0/6		100%	3.55[0.12,105.82]
Subtotal (95% CI)	**6**	**6**		**100%**	**3.55[0.12,105.82]**
Total events: 1 (Gestrinone 2.5mg), 0 (Gestrinone 1.25mg)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
5.3.3 discontinued treatment because of continuing pain					
Hornstein 1990	0/6	1/6		100%	0.28[0.01,8.42]
Subtotal (95% CI)	**6**	**6**		**100%**	**0.28[0.01,8.42]**
Total events: 0 (Gestrinone 2.5mg), 1 (Gestrinone 1.25mg)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
5.3.4 suffered from irregular bleeding					
Hornstein 1990	4/6	5/6		100%	0.4[0.03,6.18]
Subtotal (95% CI)	**6**	**6**		**100%**	**0.4[0.03,6.18]**
Total events: 4 (Gestrinone 2.5mg), 5 (Gestrinone 1.25mg)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					



Favours 2.5mg — Favours 1.25mg

APPENDICES

Appendix 1. MDSG search string

MDSG Search String for AP601 21.11.08

Keywords CONTAINS "endometriosis" or "adenomyosis" or "pelvic pain" or "dyschezia" or "dyspareunia" or Title CONTAINS "endometriosis" or "adenomyosis" or "pelvic pain" or "dyschezia" or "dyspareunia"

AND

Keywords CONTAINS "progestagen" or "Progestagen antagonists" or "Progestagen only" or "progestin" or "progestins" or "progestogen" or "progestogens" or "noresthisterone" or "norethindrone" or "norethindrone acetate" or "Norethisterone" or "norethisterone acetate" or "Norgestimate" or "Norgestrel" or "lynestrenol" or "lynestrol" or "medroxyprogesterone" or "Medroxyprogesterone Acetate" or "dydrogesterone" or "dydrogestrone" or Title CONTAINS"progestagen" or "Progestagen antagonists" or "Progestagen only" or "progestin" or "progestins" or "progestogen" or "progestogens" or "noresthisterone" or "norethindrone" or "norethindrone acetate" or "Norethisterone" or "norethisterone acetate" or "Norgestimate" or "Norgestrel" or "lynestrenol" or "lynestrol" or "medroxyprogesterone" or "Medroxyprogesterone Acetate" or "dydrogesterone" or "dydrogestrone"

Appendix 2. CENTRAL search string

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:
---
1 endometriosis.mp. or exp Endometriosis/ (751)
2 dysmenorrhea.mp. or exp Dysmenorrhea/ (590)
3 dyspareunia.mp. or exp Dyspareunia/ (208)
4 dyschezia.mp. (8)
5 adenomyosis.tw. (27)
6 (pelvi$ adj2 pain$).tw. (410)
7 or/1-6 (1700)
8 exp progestins/ or exp desogestrel/ or exp dydrogesterone/ or exp gestrinone/ (1683)
9 progestin$.tw. (811)
10 desogestrel.tw. (360)
11 dydrogesterone$.tw. (145)
12 gestrinone$.tw. (48)
13 (progestagen$ or progestogen$).tw. (693)
14 norethisterone$.mp. or exp Norethindrone/ (891)
15 exp medroxyprogesterone/ or exp medroxyprogesterone 17-acetate/ (984)
16 medroxyprogesterone$.tw. (1238)
17 norethynodrel.mp. or exp Norethynodrel/ (11)
18 lynestrenol.mp. or exp Lynestrenol/ (71)
19 (anti-progestagen$ or antiprogestagen$).mp. (5)
20 anti-progestogen$.tw. (2)
21 antiprogestogen$.mp. (7)
22 duphaston.tw. (4)
23 or/8-22 (4509)
24 7 and 23 (184)
25 limit 24 to yr="2010 -Current" (6)

Appendix 3. MEDLINE search string

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1948 to Present>
Search Strategy:
---
1 endometriosis.mp. or exp Endometriosis/ (17589)
2 dysmenorrhea.mp. or exp Dysmenorrhea/ (4047)
3 dyspareunia.mp. or exp Dyspareunia/ (2588)
4 dyschezia.mp. (142)
5 adenomyosis.tw. (1436)
6 (pelvi$ adj2 pain$).tw. (5215)
7 or/1-6 (26856)
8 exp progestins/ or exp desogestrel/ or exp dydrogesterone/ or exp gestrinone/ (57985)

9 progestin$.tw. (9268)
10 desogestrel.tw. (946)
11 dydrogesterone$.tw. (340)
12 gestrinone$.tw. (156)
13 (progestagen$ or progestogen$).tw. (6247)
14 norethisterone$.mp. or exp Norethindrone/ (4378)
15 exp medroxyprogesterone/ or exp medroxyprogesterone 17-acetate/ (6287)
16 medroxyprogesterone$.tw. (5014)
17 norethynodrel.mp. or exp Norethynodrel/ (999)
18 lynestrenol.mp. or exp Lynestrenol/ (992)
19 (anti-progestagen$ or antiprogestagen$).mp. (82)
20 anti-progestogen$.tw. (10)
21 antiprogestogen$.mp. (45)
22 duphaston.tw. (32)
23 or/8-22 (75336)
24 7 and 23 (1805)
25 randomized controlled trial.pt. (315054)
26 controlled clinical trial.pt. (83234)
27 randomized.ab. (230445)
28 placebo.tw. (135397)
29 clinical trials as topic.sh. (157382)
30 randomly.ab. (169316)
31 trial.ti. (98595)
32 (crossover or cross-over or cross over).tw. (51776)
33 or/25-32 (771481)
34 exp animals/ not humans.sh. (3654092)
35 33 not 34 (712452)
36 24 and 35 (265)
37 (201011$ or 201012$).ed. (130524)
38 2011$.ed. (684762)
39 37 or 38 (815286)
40 36 and 39 (12)

Appendix 4. EMBASE search string

Database: Embase <1980 to 2011 Week 33>
Search Strategy:
---

1 exp ENDOMETRIOSIS/ (19333)
2 Endometrio$.tw. (20543)
3 exp DYSMENORRHEA/ (6131)
4 dysmenorrh$.tw. (3937)
5 exp DYSPAREUNIA/ (3928)
6 dyspareunia.tw. (2704)
7 dyschezia.tw. (191)
8 adenomyosis.tw. (1752)
9 (pelvi$ adj2 pain$).tw. (6579)
10 or/1-9 (39304)
11 exp gestagen/ (121541)
12 exp DESOGESTREL/ (2475)
13 exp DYDROGESTERONE/ (1264)
14 exp GESTRINONE/ (502)
15 gestagen$.tw. (1570)
16 progestin$.tw. (9324)
17 desogestrel.tw. (999)
18 dydrogesterone$.tw. (393)
19 gestrinone$.tw. (171)
20 (progestagen$ or progestogen$).tw. (6301)
21 exp NORETHISTERONE/ (6121)
22 norethisterone.tw. (1683)
23 exp MEDROXYPROGESTERONE/ (4057)
24 exp medroxyprogesterone acetate/ (12602)

25 medroxyprogesterone$.tw. (5120)
26 norethynodrel.tw. (212)
27 exp noretynodrel/ (1199)
28 exp LYNESTRENOL/ (1649)
29 lynestrenol.tw. (235)
30 (anti-progestagen$ or antiprogestagen$).tw. (87)
31 (anti-progestogen$ or antiprogestogen$).tw. (55)
32 duphaston.tw. (405)
33 or/11-32 (124641)
34 10 and 33 (4547)
35 Clinical Trial/ (812775)
36 Randomized Controlled Trial/ (284865)
37 exp randomization/ (53586)
38 Single Blind Procedure/ (13869)
39 Double Blind Procedure/ (99784)
40 Crossover Procedure/ (30324)
41 Placebo/ (182799)
42 Randomi?ed controlled trial$.tw. (62548)
43 Rct.tw. (7368)
44 random allocation.tw. (1037)
45 randomly allocated.tw. (15261)
46 allocated randomly.tw. (1682)
47 (allocated adj2 random).tw. (685)
48 Single blind$.tw. (10902)
49 Double blind$.tw. (116791)
50 ((treble or triple) adj blind$).tw. (241)
51 placebo$.tw. (157523)
52 prospective study/ (168438)
53 or/35-52 (1129836)
54 case study/ (13016)
55 case report.tw. (204554)
56 abstract report/ or letter/ (788071)
57 or/54-56 (1001709)
58 53 not 57 (1096687)
59 34 and 58 (1234)
60 (201011$ or 201012$).em. (38101)
61 2011$.em. (786910)
62 60 or 61 (825011)
63 59 and 62 (70)

Appendix 5. PsycINFO search string

Database: PsycINFO <1806 to August Week 3 2011>
Search Strategy:
---

1 endometrio$.tw. (136)
2 exp Dysmenorrhea/ (151)
3 dysmenorrh$.tw. (280)
4 dyspareunia.tw. (369)
5 dyschezia.tw. (3)
6 adenomyosis.tw. (5)
7 (pelvi$ adj2 pain$).tw. (352)
8 exp Progestational Hormones/ (1785)
9 progestin$.tw. (445)
10 desogestrel.tw. (6)
11 dydrogesterone$.tw. (9)
12 gestrinone$.tw. (0)
13 (progestagen$ or progestogen$).tw. (147)
14 medroxyprogesterone$.tw. (209)
15 exp progesterone/ (1624)
16 norethisterone$.tw. (16)
17 norethynodrel.tw. (7)

18 lynestrenol.tw. (4)
19 (anti-progestagen$ or antiprogestagen$).tw. (2)
20 anti-progestogen$.tw. (0)
21 antiprogestogen$.tw. (0)
22 duphaston.tw. (0)
23 or/1-7 (1066)
24 or/8-22 (2177)
25 23 and 24 (12)
26 limit 25 to yr="2010 -Current" (2)

WHAT'S NEW

Date	Event	Description
16 February 2012	New citation required but conclusions have not changed	Included studies have not led to change in conclusions
29 August 2011	New search has been performed	We have included six new studies in this update (Bergvist 2001; Harada 2009; Razzi 2007; Schlaff 2006; Strowitzki 2010; Vercellini 2002)

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 2, 2000

Date	Event	Description
7 November 2008	Amended	Converted to new review format.
17 January 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julie Brown was involved in identifying studies, data extraction, final formatting of the review and writing the final draft.

Sari Kives contributed to writing some of the review and in identifying studies and data extraction.

Muhammad Akhtar reviewed the review and made contributions to the implications for practice.

Previous authors, including Andrew Prentice, Alison Deary and Elaine Bland, were involved in the original review.

DECLARATIONS OF INTEREST

AJD was partly employed on a non-conditional educational grant from Zeneca Pharma. The grant was utilised to provide a telephone support line for endometriosis patients attending a tertiary specialist clinic.

SOURCES OF SUPPORT

Internal sources

- University of Cambridge, UK.

External sources

- The Cambridge University Hospital's NHS Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [therapeutic use]; Dydrogesterone [therapeutic use]; Endometriosis [complications] [*drug therapy]; Gestrinone [therapeutic use]; Gonadotropin-Releasing Hormone [analogs & derivatives]; Leuprolide [therapeutic use]; Medroxyprogesterone Acetate [therapeutic use]; Pelvic Pain [*drug therapy] [etiology]; Progesterone Congeners [*therapeutic use]; Progestins [*antagonists & inhibitors]

MeSH check words

Female; Humans